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INCOMPATIBILITY OF MOTHER AND FOETUS WITH RESPECT TO THE ISO-AGGLUTINOGEN A AND ITS ANTIBODY

BY

JOHN A. H. WATERHOUSE, M.A., Ph.D.

AND

LANCELOT HOGBEN, F.R.S.

1. Introduction

Recent research on the Rh antigen discovered by Landsteiner and Wiener (1940) has provided conclusive evidence pointing to the occurrence of maternal iso-immunization—i.e. the production of antibodies by the mother in response to the presence of corpuscular antigens in the foetus. Maternal iso-immunization throws new light on the occurrence of neonatal haemolytic anaemias, of stillbirths, and of abortions in sibships containing members so affected. The importance of its contribution to neonatal and foetal death naturally prompts us to ask to what extent: (*a*) other foetal antigens evoke the production of maternal antibodies; (*b*) other maternal antibodies may penetrate the placental barrier with lethal or semi-lethal consequences to the foetus or newly born.

These issues had in fact provoked attention before work on the *Rhesus* antigen clarified current views. Diamond, Blackfan, and Baty (1932) and independently Parsons, Hawksley, and Gittins (1933) suggested that hydrops foetalis, icterus gravis neonatorum, and anaemia of the newborn are different manifestations of the same disease, which they called erythroblastosis foetalis. As the name suggests, its characteristic feature is excess of immature red blood cells in the blood of the foetus. The reason for this remained unexplained until 1940. In 1939 Levine and Stetson described an unusual case of intra-group agglutination in which a woman just delivered of a macerated stillborn foetus was transfused with blood from her husband of the same iso-agglutinogen group (O). Shortly after this she showed all symptoms of incompatible transfusion. Other tests subsequently proved that her serum agglutinated her husband's cells, though she was later transfused with blood from donors of group O whose cells did not agglutinate in this way. Tests on a number of group O donors, to find a miscible blood, showed that only 20% were indeed compatible. Levine and Stetson made further tests, and showed that such agglutination was due to an irregular iso-agglutinin independent of the factors M, N, or P, but were unable to obtain a

sufficient quantity of the serum to test the incidence in groups A, B, etc. These examples of immediate reactions following post-partum transfusion have been recorded several times and are not easily explicable on the hypothesis that the woman had developed antibodies to an unusual agglutinogen in blood from a previous transfusion. Levine and his co-workers—Levine, Burnham, Katzin, and Vogel (1941), Levine (1943)—suggested that the foetus inherits in such cases from the father a dominant gene responsible for the production of an antigen which passes through the placenta and stimulates the mother to produce antibodies also placenta-diffusible and hence of evoking haemolysis in the foetus. The case mentioned above and those reported by Levine and Katzin (1940) were shown to be due to the antigen which reacts to serum of rabbits immunized to blood cells of the *Rhesus* monkey.

Implicit in this interpretation is a postulate, the importance of which was first emphasized by Haldane (1942)—viz. that the placentae of *some*, but not all, women are permeable to antigens and some antibodies. This exposes a vista of new possibilities. Prior to this demonstration of iso-immunization by the Rh antigen as a major circumstance contributory to erythroblastosis foetalis, several writers —Hirszfeld (1928) in particular—had suggested that blood-group incompatibility between mother and foetus with respect to the A-B-O series might be the cause of foetal death and severe jaundice. Hirszfeld used the term " heterospecific pregnancies " to denote such cases of incompatibility and endeavoured to demonstrate the fact by determining relative birth-weights. After the general adoption of Bernstein's triple allelomorph theory of the inheritance of the A-B-O groups, Hirszfeld neglected to follow up this suggestion, though he had in fact observed (1925) that there are less A children from matings A father by O mother than from the reciprocal matings. Nearly twenty years elapsed before the elucidation of the Rh antigen prompted Levine (1943) to a preliminary review of seven published studies on the A-B-O group.

Levine's review is suggestive, but by no means conclusive, with respect to the thesis advanced—that is to say, the possibility that the antibody for the antigen A, present in the serum of a mother of group O, may diffuse through the placenta into the circulation of a foetus which itself belongs to group A. The consequences need not be identical with those characteristic of erythroblastosis foetalis, but may be none the less disastrous to the foetus on that account. Accordingly, certain phenotypic mother–child combinations with respect to the A-B-O grouping might be associated with high foetal or neonatal mortality. For instance, there should then be a deficiency of A offspring of unions between a father A and a mother O, but no corresponding deficiency with respect to A offspring of the reciprocal mating. This was in essence the test which Levine applied. The object of the present enquiry is to explore the significance of disparities of this sort more extensively.

The table Levine has published summarizes 8 studies. Of these he claims that 7 " confirm the concept of selective foetal death by iso-immunization ". We

have not been able to obtain access to Hirszfeld's or to Clausen's studies in present circumstances, and one of Levine's samples is based on his own unpublished results. Reference to the original sources of the remainder does not in all cases confirm Levine's figures. A recalculation of the data based on the relations shown on p. 4 appears in Table I, in which Levine's figures are in parentheses. The gene frequencies used were obtained by successive approximation in three stages—first from the square root formulae (p. 4), then from the Bernstein modifications, and finally from the quartic maximum likelihood equations. It is noteworthy that results of only three studies yield satisfactory confirmation of Levine's hypothesis. One is inconclusive and the other (Vuori) points decisively to the opposite conclusion. Vuori's result may conceivably be due to a clerical error, since such errors are not entirely absent from his tables.

TABLE I

		% A		△	n	t	P	N
Hirszfeld (1928) (15 authors)	O×A		(65·1)					
	A×O		(56·0)					
Hirszfeld and Hirszfeld (1928)	O×A	66·18	(63·1)	−4·095	68	1·045	0·3	730
	A×O	57·63	(60·5)	1·491	59	0·392	0·7	
Landsteiner and Levine (1928)	O×A	60·56	(60·6)	−5·15	142	0·881	0·4	1,047
	A×O	45·3	(44·8)	13·62	117	2·522	0·01	
Wiener and Vaisberg (1931) (whites only)	O×A	59·02	(54·8)	−1·936	122	0·355	0·72	807
	A×O	46·99	(52·5)	8·667	83	1·901	0·06	
Clausen (1934)	O×A		(66·3)					
	A×O		(62·0)					
Vuori (1930)	O×A	48·67	(46·7)	14·718	150	2·398	0·02	1,774
	A×O	64·24	(63·8)	−8·698	151	1·472	0·15	
Landsteiner and Wiener (1941) (whites only)	O×A	68·42	(68·4)	−5·23	56	1·480	0·17	342
	A×O	25·00	(25·0)	6·85	20	3·527	0·003	
Levine and Landsteiner (unpublished data)	O×A		(77·1)					
	A×O		(45·2)					

% A = Percentage of A offspring from mating class (figures in brackets from Levine, 1943).
△ = Deficiency in observed A offspring over calculated.
n = Number of offspring in mating class.
t = Ratio of △ to standard deviation of mating class.
P = Probability that observed difference is due to chance.
N = Total number of persons (parents and offspring) in whole investigation.

2. Composition of Data for this Enquiry

In what follows the convention adopted is to denote the male partner as the first and the female as the second—i.e. O.A means the mating of a father group O

with a mother group A, and A.O means the mating of a father of group A with a mother of group O. A preliminary analysis exhibited in Table III refers to studies already tabulated in Lattes (1932), who does not separately record offspring of O.A and A.O. This table refers only to studies based on 1,000 or more parents and children and excludes earlier and therefore less reliable samples even if so large. Since we cannot here compare deficiency with respect to the expectation of A offspring in the reciprocal matings mentioned we can only apply a cruder test, that is to say, determine whether the observed proportion of A offspring is in fact deficient. The calculation of expectation is based on Bernstein's method with the usual symbols, viz.:

(i) (A), (B), (O) for the phenotypic frequencies;

(ii) a, b, r, for the corresponding gene frequencies, connected by the relation:

$$a = 1 - \sqrt{(O)+(B)}$$
$$b = 1 - \sqrt{(O)+(A)}$$
$$r = \sqrt{(O)}$$

On the assumption that all phenotypes are equally viable, the expectations of offspring of the several possible unions in a population mating at random are as shown in Table II.

TABLE II

Mating	O	A	B	AB
O×O	1	0	0	0
O×A	$\frac{r}{a+2r}$	$\frac{a+r}{a+2r}$	0	0
O×B	$\frac{r}{b+2r}$	0	$\frac{b+r}{b+2r}$	0
O×AB	0	$\frac{1}{2}$	$\frac{1}{2}$	0
A×A	$\frac{r^2}{(a+2r)^2}$	$\frac{(a+r)(a+3r)}{(a+2r)^2}$	0	0
A×B	$\frac{r^2}{(a+2r)(b+2r)}$	$\frac{r(a+r)}{(a+2r)(b+2r)}$	$\frac{r(b+r)}{(a+2r)(b+2r)}$	$\frac{(a+r)(b+r)}{(a+2r)(b+2r)}$
A×AB	0	$\frac{a+2r}{2a+4r}$	$\frac{r}{2a+4r}$	$\frac{a+r}{2a+4r}$
B×B	$\frac{r^2}{(b+2r)^2}$	0	$\frac{(b+r)(b+3r)}{(b+2r)^2}$	0
B×AB	0	$\frac{r}{2b+4r}$	$\frac{b+2r}{2b+4r}$	$\frac{b+r}{2b+4r}$
AB×AB	0	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{2}$

It should be emphasized that expectations calculated on this basis imply the qualification stated above—i.e. equal viability of the phenotypes. Hence if the phenotype A were in fact slightly more viable than O, failure to detect a deficiency of individuals of group A would not necessarily disprove the hypothesis under examination. This is one possible explanation of the lack of any clear indications in support of the hypothesis furnished by the figures in Table III.

TABLE III

Author	N	% Deficiency of A	n
Snyder	1,095	−14·3	264
Furuhata	3,962	6·5	471
Sievers	1,394	6·1	218
Thomson	1,303	1·0	171
Hazelhorst	3,024	3·0	349
Landsteiner and Levine ..	1,017	− 3·0	230
Kossovitch	966	− 1·6	217
Vuori	1,777	3·4	301
Ichida	1,681	8·0	233
Wiener and Vaisberg ..	1,007	3·8	223

N=Total number of persons (parents and children) in whole investigations.
n=Number of children in mating class (O×A).

Of the 10 studies here exhibited, 7 provide evidence of deficiency with respect to offspring of group A—a fact which would be suggestive were it not for the magnitude of the excess of Snyder's careful study. It is difficult to assess the importance of this discrepancy with justice. Although Snyder carried out his serological tests with the utmost circumspection, analysis of his figures by the χ^2test shows that they do not refer to a homogeneous population mating at random.

Since evidence provided by examination of the correspondence between observed and expected numbers of A offspring in a mixed assembly of parents of whom one belongs to group O and one to group A fails to provide the decisive test of the hypothesis of iso-immunization as applied to the A-B-O grouping, it remains to examine two possibilities: (*a*) whether the proportion of A offspring in O.A matings exceeds that of the reciprocal union; (*b*) whether the proportion of A offspring in A.O as opposed to O.A matings falls off with increasing birth rank in such a way as to indicate an increasing titre of anti-A in the maternal circulation as the result of previous production of the antibody in response to the presence of an A foetus *in utero*.

It is clear that a conclusive answer to the question raised by Levine calls either for re-investigation by recourse to a large pool of new material, or for examination of available data separable into sibships of matings O.A and A.O. An *ad hoc* investigation would be protracted and laborious. In the absence of new evidence any examination of available documentary evidence which conforms to the requirements stated should restrict itself to the subject matter of more recent inquiries

undertaken with due regard to the pitfalls which beset pioneer work, and based on samples which we may plausibly ascribe to a homogeneous population mating at random. Accordingly, we have arbitrarily rejected all data published before 1927 and selected from accessible literature after that date only such accounts as conform to other requirements stated above, rejecting those that do not provide explicit family data on such relevant issues as order of birth. Of about forty studies examined only 12, as listed below, satisfy all these requirements.

Sample No.	No. of Families	No. of Children	Author
1	150	430	Hirszfeld and Hirszfeld (1927)
2	166	715	Landsteiner and Levine (1928)
3	118	571	Wiener and Vaisberg (1931)
4	68	215	Schiff and Sasaki (1932)
5	100	219	Hyman (1935)
6	56	205	Zieve, Wiener, and Fries (1936)
7	50	157	Matta (1937)
8	112	433	Dahr (1940)
9	58	226	Landsteiner and Wiener (1941)
10	235	595	Taylor and Prior (1938); Race, Ikin, Taylor, and Prior (1942)
11	40	138	Wiener and Sonn (1943)
12	86	235	Wiener, Sonn, and Belkin (1944)

The first investigation listed—that of the Hirszfelds—was undertaken to explore a possible relationship between the A-B-O blood groups and immunity to diphtheria and scarlet fever by recourse to the tests of Schick and Dick. It is a very complete sample, since it gives the age, blood group, and sex of parents and children for each family. Landsteiner and Levine (2) were investigating the heredity of the M and N groups in the U.S.A. They also give the blood group and sex of parents and children in order of birth, as do Wiener and Vaisberg (U.S.A.) in a similar study with the same end in view. Both of these studies include coloured families—20 in the first and 13 in the second—though not distinguished as such by Landsteiner and Levine. Wiener and Vaisberg do so, and we have rejected these in our analysis of their data. Schiff and Sasaki (Berlin) again give sex and blood group of parents and children, together with M N type, and the " secretor " property. Hyman (U.S.A.), studying the inheritance of the M and N factors, gives blood group and sex throughout, while Zieve, Wiener, and Fries (U.S.A.) give, in a very detailed family study on the inheritance and linkage relations of allergic disease,

for each person the age, sex, blood group, M N type, whether or not allergic, and occasionally the secretor type. Matta, working in Glasgow, examined a number of families serologically, and lists his results separately for each family, distinguishing the sex of the parents but not of the children. His book gives the results of another study done in Cairo. Unfortunately, this is incomplete from the point of view of this investigation. Not infrequently it cites only one parent. Examination of the residual data by the χ^2 test showed that the sample was not random. Hence it was necessary to reject it. Dahr (Germany) was investigating the heredity of the factor P, and gave at the same time the A-B-O groups and M N types, with sex of parents and children. This was the latest German sample available. The English sample (10) was collected to investigate the distribution and heredity of both the A_1-A_2 and the M N types. It gives the sex of parents and children. The latest three samples of the first group, Landsteiner and Wiener (9), Wiener and Sonn (11) and Wiener, Sonn, and Belkin (12), all from the U.S.A., were undertaken to investigate the genetics of the Rh factor and its subgroups, but record A-B-O and M N determinations together with the sex of parents and children. In our analysis below, coloured families have been omitted from the two of these samples which contained them.

Table IV gives the percentage distribution of the blood groups of parents and children in these studies (P=parents, C=children). With due regard to such variations as arise from small sample size, the group as a whole is fairly homogeneous; and the distribution of the children closely resembles that of their parents —an indication of genetic equilibrium in the population.

TABLE IV

% Distribution of A-B-O Blood Groups

Sample No.	No. of Parents	No. of Children	O		A		B		AB	
			P	C	P	C	P	C	P	C
1	300	430	36·67	36·51	44·00	43·26	11·33	12·09	8·00	8·14
2	332	715	45·18	48·39	35·84	34·82	15·36	12·17	3·61	4·62
3	236	571	43·64	46·41	37·71	36·43	13·56	12·61	5·08	4·55
4	136	215	44·12	36·28	37·50	48·37	11·76	11·16	6·62	4·19
5	200	219	46·00	45·66	41·00	39·27	8·50	8·22	4·50	6·85
6	112	205	36·61	40·98	45·54	44·39	16·07	9·76	1·79	4·88
7	100	157	46·00	40·76	40·00	43·31	9·00	10·19	5·00	5·73
8	224	433	44·20	41·11	41·96	44·57	9·38	11·55	4·46	2·77
9	116	226	38·79	38·94	41·38	44·25	12·07	12·39	7·76	4·42
10	470	595	45·11	47·39	41·91	37·65	10·64	10·42	2·34	4·54
11	80	138	38·75	37·68	43·75	47·10	11·25	13·04	6·25	2·17
12	172	235	44·19	41·28	36·63	44·68	11·05	11·06	8·14	2·98

Tables V and VI respectively summarize the numbers of families and children in each of the 16 mating classes. The total number of families extracted from these

12 investigations is 1,239, and the total number of children 4,139. Although these figures result from a summary of samples having different individual distributions, and cannot therefore be regarded strictly as from a homogeneous sample, reciprocal mating groups may legitimately be compared, since for each sample, as for the sum, the expectation is equal in each group. Thus the most significant departures from equality occur in the reciprocal groups O.A and A.O, and in O.B and B.O,

TABLE V
No. of Families

Sample No.	O.O	O.A	A.O	O.B	B.O	O.AB	AB.O	A.A	A.B	B.A	A.AB	AB.A	B.B	B.AB	AB.B	AB.AB	Total
1	22	23	22	11	4	4	2	30	9	9	6	3	0	1	0	4	150
2	32	32	25	11	12	3	3	18	12	10	0	4	3	0	0	1	166
3	24	23	18	3	8	1	2	15	5	7	5	1	3	2	1	0	118
4	13	16	13	0	3	1	1	4	4	5	4	1	1	1	1	0	68
5	21	21	20	5	2	0	2	14	4	6	2	1	0	0	0	2	100
6	9	7	11	0	5	0	0	12	4	3	0	2	3	0	0	0	56
7	11	7	8	2	5	1	1	11	1	1	1	0	0	0	0	1	50
8	23	24	18	3	4	3	1	22	3	3	1	1	2	2	2	0	112
9	8	12	6	3	5	0	3	10	4	1	2	3	0	1	0	0	58
10	45	52	46	9	12	1	2	37	9	11	4	1	3	1	2	0	235
11	4	11	6	3	1	2	0	6	3	0	2	1	1	0	0	0	40
12	13	16	16	4	5	3	6	10	5	3	1	2	1	0	0	1	86
TOTAL	225	244	209	54	66	19	23	189	63	59	28	20	17	8	6	9	1,239

TABLE VI
No. of Children

Sample No.	O.O	O.A	A.O	O.B	B.O	O.AB	AB.O	A.A	A.B	B.A	A.AB	AB.A	B.B	B.AB	AB.B	AB.AB	Total
1	65	68	59	24	12	13	3	94	24	28	19	8	0	4	0	9	430
2	136	142	117	49	49	10	13	78	47	43	0	17	10	0	0	4	715
3	121	122	83	10	40	6	11	60	25	35	25	6	12	10	5	0	571
4	35	54	45	0	7	2	5	13	7	21	14	3	3	4	2	0	215
5	46	40	41	12	4	0	5	35	8	19	3	2	0	0	0	4	219
6	42	34	40	0	13	0	0	39	15	7	0	6	9	0	0	0	205
7	38	18	20	7	14	2	7	33	2	5	5	0	0	0	0	6	157
8	86	81	85	9	18	12	5	79	13	14	4	5	12	6	4	0	433
9	28	56	20	12	19	0	7	45	9	3	5	20	0	2	0	0	226
10	128	132	106	28	34	2	2	77	23	29	12	3	12	4	3	0	595
11	14	36	21	11	7	6	0	20	11	0	6	3	3	0	0	0	138
12	40	52	49	9	12	3	14	26	12	6	3	7	1	0	0	1	235
TOTAL	779	835	686	171	229	56	72	599	196	210	96	80	62	30	14	24	4,139

where the observed numbers of children are respectively 835: 686, and 171: 229. If we regard the mean as the expected number of children, and calculate the probability of observed deviations therefrom we get:

O.A $t=3\cdot82$, $n=1{,}521$, $P<\cdot001$
O.B $t=2\cdot9$, $n=400$, $P=0\cdot0035$

There is thus a highly significant deficiency of A.O compared with O.A children (and families). As will appear later, this is almost entirely attributable to selective loss of A children from matings A.O. For the matings O.B and B.O, there is a deficiency of O.B families and children. This too is largely attributable to selective loss of B children. Evidently, the mechanism of this loss is not comparable to that of A children in A.O families.

3. Genetic Analysis of the Samples

Of matings which are relevant to the end in view, only A.O and O.A need concern us. On the assumption that such incompatibility militates against the viability of children of group A by mothers of group O the hypothesis of mother–foetus incompatibility with respect to the A antigen is susceptible of more than one line of attack. At the same time it implies: (*a*) that the net fertility of matings A.O is less than that of O.A; (*b*) that the observed offspring of group A in matings A.O falls short of expectation to a greater extent than in matings O.A.

We may examine the data in Table VII from either viewpoint. To say that (*a*) is correct means that the ratio of the total number of offspring whose parents are A.O to the total number of offspring whose parents are O.A is less than unity. This statement is of course independent of whether we are considering individual homogeneous samples or a congeries of such samples. That is to say, it is equally applicable to the grand total of data such as those in Tables VII and VIII, as to those of the individual studies there exhibited; and the cogency of a conclusion derived from the summation of the data is not diminished by uncertainty with respect to the significance of the individual items, since the magnitude of the effect may be such as to be manifest only of a gross sample larger than our individual subsamples. The same considerations apply *mutatis mutandis* to a second implication of (*a*). If the fertility of A.O is less than that of O.A matings, there will be more childless unions of the type A.O than of the type O.A. Hence the total number of families with parents O.A should significantly exceed those with parents A.O.

As regards the number of families respectively with parents A.O and O.A Table VII shows that the number of those with a male parent of group A is deficient in 9 out of the 12 samples, and excessive in two only. For the entire group of 453 families the observed proportions with one parent of group O and one of group A we have:

O.A	$53\cdot9\pm2\cdot3\%$
A.O	$46\cdot1\pm2\cdot3\%$
Difference	$7\cdot8\pm3\cdot3\%$

Thus the deficiency with respect to A.O families is more than twice its standard error. The discrepancy between the total numbers of children in the two groups is even more striking. The deficiency of A.O children is over 5 times its standard error, and is therefore highly significant. The actual proportions of children of one or other mating in the two classes are:

O.A $54{\cdot}9 \pm 1{\cdot}3\%$
A.O $45{\cdot}1 \pm 1{\cdot}3\%$
Difference $9{\cdot}8 \pm 1{\cdot}8\%$

TABLE VII

Sample No.	No. of Families		No. of Children		Mean No. of Children per family	
	O.A	A.O	O.A	A.O	O.A	A.O
1	23	22	68	59	2·96	2·68
2	32	25	142	117	4·44	4·68
3	23	18	122	83	5·30	4·61
4	16	13	54	45	3·38	3·46
5	21	20	40	41	1·90	2·05
6	7	11	34	40	4·86	3·64
7	7	8	18	20	2·57	2·50
8	24	18	81	85	3·38	4·72
9	12	6	56	20	4·67	3·33
10	52	46	132	106	2·54	2·31
11	11	6	36	21	3·27	3·50
12	16	16	52	49	3·23	3·06
TOTAL	244	209	835	686	3·42	3·28

TABLE VIII

Sample	$\frac{\text{O.A}}{\text{A.O}}$ Fams.	$\frac{\text{O.A}}{\text{A.O}}$ Chil.	O.A	A/O ratio Exp.	A.O
1	1·05	1·15	1·96	1·48	1·36
2	1·28	1·21	1·54	1·34	0·83
3	1·28	1·47	1·44	1·36	0·88
4	1·23	1·20	1·45	1·36	4·00
5	1·05	0·98	1·22	1·37	1·54
6	0·64	0·85	1·00	1·50	2·64
7	0·88	0·90	8·00	1·38	1·86
8	1·33	0·95	1·89	1·40	1·36
9	2·00	2·80	2·30	1·45	0·33
10	1·13	1·25	1·44	1·39	1·72
11	1·83	1·71	1·40	1·46	1·33
12	1·00	1·06	1·89	1·35	0·96
TOTAL	1·17	1·22	1·62		1·28

The right-hand half of Table VIII shows data relevant to (*b*) above. On the assumption of equal viability and random mating, the expected A/O ratio of children is the same for sibships with parents A.O and O.A, viz.:

$$\frac{(a+r)}{r}=\sqrt{1+\frac{(A)}{(O)}}$$

For the O.A group, 9 samples out of 12 have sibs belonging to group A in excess of expectation and for the A.O group only 5. The proportion of A offspring in O.A families exceeds that in A.O families in 8 of the samples. Of itself, this is not conclusive; but we can probe the issue further by an examination of the data in other ways which permit us to pool the data of the 12 samples. We may first ask how far the net excess of A children in O.A families contributes to the excess of the total number of offspring in such families. The relevant figures are as follows:

Parents	No. of Children		Total
	O	A	
O.A ..	320	515	835
A.O ..	301	385	686

The net excess of A children in O.A families is thus $515-385=130$. The excess of total children is $835-686=149$. So the deficiency of A children in A.O families tallies closely with the lower fertility of such families.

We can also select from our data a class of families which we are entitled to pool. If the parent of group A is known to be heterozygous in virtue of having one or more children of group O, the expected ratio of children of group A to children of group O in matings of either type under discussion does not depend on the gene frequencies *a* and *r*. Accordingly such samples are on all fours, and we can combine our data to test for the discrepancy between the observed and expected A/O ratio. If the two phenotypes are equally viable, the expected ratio is unity. Since the probability of getting a child of group O from matings O.A or A.O when the parent of group A is heterozygous is 0·5, it is quite possible for all children of such parents to be of group A or all of group O. If all are of group A we have no means of deciding whether the parent of group A is himself or herself heterozygous. This is of course an outstanding statistical problem of human genetics arising from the small size of the human family. Two well-known methods, respectively called the " sib " and the " familial ", have been devised for factorial analysis of human data with due regard to its relevance, especially in connection with familial traits—i.e. such as

turn up commonly among several sibs of parents who are themselves normal, hence putatively both heterozygous. For the particular class of matings involving one recessive and one heterozygous parent an alternative procedure is open. If p and q respectively stand for the probabilities that an individual will be of the recessive and dominant phenotype, the respective probabilities that a sibship of s members will be exclusively composed of one or the other are p^s and q^s. For unions of one heterozygous and one homozygous parent, $p=\frac{1}{2}=q$, and $p^s=q^s$. In other words, sibships with only recessive offspring and sibships with offspring of only the dominant phenotype will occur with equal frequency in such matings. In making the judgment that the parent of the dominant phenotype is heterozygous we have to exclude from our sample all sibships exclusively composed of the dominant phenotype. The preceding considerations show that we can compensate for this act of selection by also excluding from our sample the corresponding number of all sibships exclusively composed of the recessive phenotype. The theoretical expectation is then what it would be if our sample were complete—i.e. $A=\frac{1}{2}=O$.

The entire group of 12 samples yielded in all 249 sibships with: (*a*) parents O.A or A.O; (*b*) at least one sib of group A and at least one sib of group O. We thus have 249 sibships with one parent of group O and one manifestly heterozygous parent of group A excluding sibships composed exclusively of individuals of group O. These families were as follows:

	No. of families	Percentage
O.A	135	54·2 ±3·2
A.O	114	45·8 ±3·2
Total	249	100
Difference ..	21	8·4 ±4·5

The composition of these families is as follows:

Parents	O	A	Total	% of A
O.A	272	278	550	50·5 ±2·1
A.O	254	209	463	45·1 ±2·3

The corresponding figures for all O.A and A.O families in the 12 samples are:

	O	A	Total	% of A
O.A	320	515	835	61·7±1·7
A.O	301	385	686	56·1±1·9

All the figures cited with respect to this selected group of families of which the A parent is heterozygous thus tally with the conclusion that A offspring of A.O unions are less viable than A offspring of O.A unions.

4. Influence of Birth Rank

By analogy with what is known of the *Rhesus* antigen, the hypothesis that the placentae of some mothers permit diffusion into the foetal circulation of the antibody for the A antigen normally present in the serum of an O mother suggests another possibility—viz. that the antigen A diffuses through the placentae of some women, and hence provokes the production of an increasing titre of the corresponding serum agglutinin (anti-A). If so, the viability of A should diminish with increasing birth rank in unions of the type A.O. Table IX presents the relevant raw data, respectively pooled from all families in the 12 samples and from such families as have a heterozygous parent of group A with at least one offspring of the same group. Table X gives the A/O ratio. For the selected group this should be 1·0 irrespective of birth rank, if both phenotypes are equally viable. It is noteworthy that the A/O ratio: (*a*) exhibits no tendency to diminish with increasing birth

TABLE IX

Offspring of groups O and A by Birth Rank

(*a*) *All families*:

Birth Rank	1		2		3		4		5		6		7		8		9		10		All	
	O	A	O	A	O	A	O	A	O	A	O	A	O	A	O	A	O	A	O	A	O	A
O×A	100	144	84	131	59	100	33	60	18	39	14	18	7	14	2	6	2	2	1	1	320	515
A×O	73	136	85	96	50	69	38	44	30	24	14	9	7	3	2	2	1	2	1	0	301	385

(*b*) *Families with one heterozygous parent of group A with at least one offspring of group A*:

	O	A	O	A	O	A	O	A	O	A	O	A	O	A	O	A	O	A	O	A	O	A
O×A	74	61	67	68	56	59	32	39	17	27	14	11	7	8	2	4	2	1	1	0	272	278
A×O	49	65	69	45	45	46	36	28	30	14	14	5	7	2	2	2	1	2	1	0	254	209

rank in families with parents O.A; (*b*) is greatest for first births in families with parents A.O, being progressively and consistently less for successive birth ranks from 3 onwards.

TABLE X

Ratio A/O Children by Birth Rank

(*a*) *All Families*:

Birth Rank	1	2	3	4	5	Over 5
O.A	1·44	1·56	1·96	1·81	2·17	1·58
A.O	1·86	1·13	1·38	1·16	0·80	0·64
(*b*) *Families with one heterozygous parent of group A with at least one offspring of group A*:						
O.A	0·82	1·00	1·05	1·21	1·59	0·92
A.O	1·33	0·65	1·02	0·78	0·47	0·44

For the families as a whole A/O is necessarily greater than unity, since its theoretical value is:

$$\frac{a+r}{r}=1+\frac{a}{r}$$

For O.A families of the selected group of the bottom half of the table, the values of this ratio fluctuate indiscriminately around 1·0 as we should expect. In the A.O families of this group it conspicuously exceeds unity only for first births.

The A/O ratio (0·65) for children of birth rank 2 is noticeably a close approximation to the reciprocal of the corresponding ratio (1·33) for birth rank 1 in the group of families with a heterozygous father having at least one offspring of group A. This relation is theoretically deducible as a consequence of the method of selecting such families for observation. Two-child families so delimited may be first O, then A, or *vice versa*. If we denote the coefficient of selection against group A for first and second pregnancies by s_1 and s_2 respectively, the proportion of survivors belonging to group A and hence of complete 2-child families of the two types specified (here denoted O: A and A: O) will be:

$$\text{O: A} \;:\; 1\text{-}s_2$$
$$\text{A: O} \;:\; 1\text{-}s_1$$

In the first birth rank the ratio A/O for *completed* 2-child families delimited as above will therefore be: $(1\text{-}s_1)\div(1\text{-}s_2)$, and the corresponding ratio for the second birth rank will be $(1\text{-}s_2)\div(1\text{-}s_1)$.

From the finite difference equation for selection of completed *c*-child families, it appears that the A/O ratio falls off less steeply as *c* increases, if we choose our families in accordance with the limitation stated above. As compared with children of higher birth rank, children of birth rank 2 are heavily weighted by

2-child families which are much more numerous than larger families in our group. This offers an explanation of what is a seemingly anomalous feature of Table X—i.e. the fact that the A/O ratio is lower for the second than for the third birth

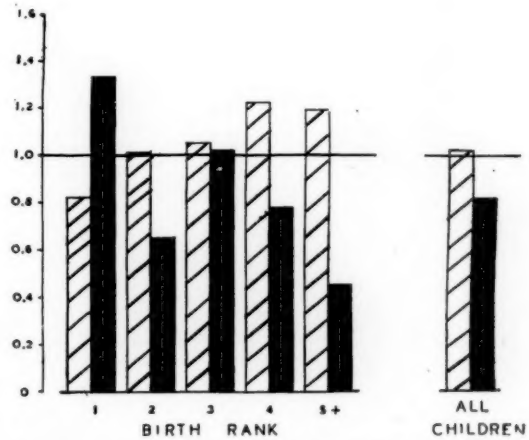

FIG. 1.—Ratio of A/O children by birth rank for families with a heterozygous parent of group A having at least one child of group A. Shaded: parents O.A. Black: parents A.O.

rank. The fact that the A/O ratio exceeds unity for the first birth rank in the selected group of families with a heterozygous male parent is also in accordance with expectation, because the method of choice excludes 1-child fraternities from the pool. We have seen that the ratio A/O for birth rank 1 in a 2-child family is $(1\text{-}s_1) \div (1\text{-}s_2)$. By hypothesis s_2 exceeds s_1, hence $(1\text{-}s_1) > (1\text{-}s_2)$ and $(1\text{-}s_1) \div (1\text{-}s_2) > 1 \cdot 0$.

5. DISCUSSION

The data examined in what has gone before consistently point to the existence of incompatibility between mothers of group O and foetuses of group A. Such incompatibility is already known to exist with respect to the Rh antigens of an Rh-positive foetus and the antibodies they may evoke in the circulation of an Rh-negative mother. This prompts us to explore the respective contributions of such incompatibilities to foetal death. The data surveyed point to a net deficiency of 25% A children in A.O matings. For a population with the genotypic frequencies definitive of the one here discussed, this would signify a foetal death rate of 8% of A children or 3% of *all* conceptions. This makes no allowance for corresponding incompatibilities with respect to the B antigen and its antibody. The figure cited is greatly in excess of present estimates of the contribution of the Rh antigens to foetal and neonatal death—i.e. about 0·5%. Our conclusion is thus contrary to the prevailing belief (see Levine, Burnham, Katzin, and Vogel, 1941; Levine, 1943; Polayes, 1945) that the mortality contribution of incompatibility with respect to the iso-agglutinin groups is trivial; but it is fully consistent

with the view that such incompatibilities do not significantly contribute to the incidence of erythroblastosis foetalis.

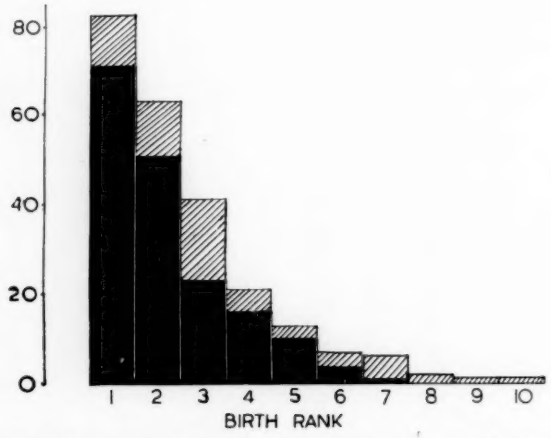

FIG. 2.—Superimposed histograms showing pooled numbers of children of group A in the twelve samples from families consisting only of children of group A respectively with parents A.O (black) and O.A (excess shaded).

6. SUMMARY

1. Levine's theory of the pathogenesis of haemolytic disease of the newborn by iso-immunization of the mother to the Rh factor on foetal erythrocytes suggests that there may be comparable intra-uterine incompatibilities of mother and foetus in particular with regard to the A-B-O groups of Landsteiner.

2. With this end in view, twelve recently published heredity studies have been selected for large size of sample, reliability of technique, and full family data.

3. The mating class A.O (father A, mother O) was chosen for special examination as the largest relevant type of union in most populations.

4. A deficiency both of families with parents A.O and of children in such families as compared with those having parents O.A (father O, mother A) has been shown to be almost entirely attributable to selective loss of children of group A.

5. Examination of the A/O ratio among children of successive birth ranks revealed a steady decline with increasing birth rank in families with parents A.O, suggestive of either: (*a*) an increasing titre of anti-A in the maternal circulation; or (*b*) increasing placental permeability with increasing maternal age.

6. The data examined and the normal presence of iso-agglutinins in blood of mothers in group O as prescribed by Landsteiner's reciprocal rule are consistent with the view that A-B-O iso-immunization acts early in foetal life to produce abortion or miscarriage, giving rise to few cases of erythroblastosis.

7. Not all families A.O are equally affected—i.e. other circumstances, such as differential placental permeability, appear to be involved.

8. A provisional estimate based upon plausible assumptions suggests that A-B-O iso-immunization is responsible for the loss of about 25% of the A children expected from marriages A×O, or about 3% of all conceptions.

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A DOCUMENTARY STUDY OF JAUNDICE ASSOCIATED WITH SYPHILIS TREATMENT AND BLOOD TRANSFUSION

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1. Introduction

A formidable problem of wartime medicine has been widespread prevalence of infective hepatitis especially in the Mediterranean zone, where it was one of the three major sources of wastage among troops. Although there was no comparable epidemic in the United Kingdom its incidence among civilians and troops alike was almost certainly much higher than in the preceding decade. A concomitant phenomenon was the occurrence of jaundice with many similar features among Army patients treated for syphilis, among individuals inoculated with vaccines containing human serum and among casualties who received blood transfusions.

Indeed, an alarming incidence of jaundice among Army syphilitics was an outstanding medical enigma of the war. To be sure, its occurrence as a complication of arsenical treatment has been recognized since 1910, but never on a comparable scale. Reliable figures for the first two years of the war are not available; but such evidence as is available suggests that its incidence rose gradually (Beattie and Marshall, 1943). By the first half of 1943 approximately 1 in 2 of all soldiers under long-term arsenic therapy developed jaundice during the course of their treatment; and by mid 1943 there was evidence to suggest that this was largely the result of infection from contaminated syringes employed for intravenous injection and venipuncture (MacCallum, 1943; Salaman *et al.*, 1944). Accordingly Army medical authorities promulgated instructions to all venereal disease treatment centres in U.K. to promote more careful sterilization of implements. Where possible syringes as well as needles were to be boiled between injections, but adaptors to prevent reflux of blood were issued as an interim measure, if shortage of syringes prevented full implementation of the policy. Meanwhile, individual treatment centres acting on their own initiative had already adopted precautionary measures.

At this time, but in a different context, the occurrence of jaundice had forced itself on the attention of the American Army Medical Service. In 1942, 28,000 cases of jaundice occurred among American troops inoculated with yellow fever vaccine containing pooled human serum as a component; but no further outbreak occurred since introduction of a new method of manufacture of the vaccine to

exclude human serum. (Circular letter of the Surgeon-General, 1942.) The Ministry of Health (1943) has summarized findings in previous outbreaks of homologous serum jaundice and has drawn attention to the danger of blood transfusion. Beeson (1943), Steiner (1943), and Morgan and Williamson (1943) have also severally reported cases of jaundice occurring in patients who had been transfused one to four months previously. The widespread occurrence of infective hepatitis at this time and clinical similarities of the several forms of jaundice encouraged the belief that delayed jaundice associated with arsenotherapy, inoculation, and blood transfusion are all manifestations of the presence of the virus responsible for infective hepatitis itself. On the other hand, there were striking discrepancies. Thus clinical experience (Pickles, 1939) ascribes the limits of the incubation period of infective hepatitis between 21 and 40 days; but that of homologous serum jaundice is decidedly more protracted. McKinlay and Truelove (1946) have brought forward other evidence pointing to the conclusion that the putative icterogenic agent of so-called post-arsphenamine jaundice is *not* the virus of infective hepatitis.

The aim of this study is to examine the documentary resources of Army statistical medicine with a view to elucidating:

(i) whether special precautions against contamination of syringes used in V.D. clinics are justified by results; and hence whether the hypothesis which attributes jaundice during treatment for syphilis to a blood-borne icterogenic agent is valid;

(ii) how far liability to jaundice during treatment for syphilis also depends on:
   (*a*) direct toxic action of arsenicals;
   (*b*) concomitant presence of *treponema pallidum*;

(iii) whether the virus of infective hepatitis is also responsible for jaundice associated with syphilis treatment and/or *delayed* jaundice following blood transfusion.

The expression *delayed* jaundice used in (iii) above signifies that cases dealt with in this communication are only such as occur after a lapse of time sufficient to exclude those due to antigen-serum incompatibilities.

2. Documentary Materials

Army medical records furnish unique opportunities for large-scale enquiries involving prolonged follow-up of patients. A central index at the War Office retains case records of all Army patients filed in order of personal number. Though a soldier may receive treatment in several hospitals all his case records are together and collectively afford a complete accessible dossier of his medical history in the Army, in so far as it involves hospital treatment. A second file of punched cards containing certain data required for routine vital statistics including personal number, diagnosis, and date of admission is also available for mechanical extraction of a nominal roll of cases of any disease over a given period. By recourse to such a roll (based on the personal numbers of the patients), it is possible to refer to the

complete record in the central index. For syphilis patients the War Office holds a supplementary file recording with relevant details all visits for out-patient treatment or surveillance. Cases of blood transfusion are not coded as such for the preparation of punched cards; but nominal rolls of battle casualties, of which a considerable proportion received such treatment, were available for this enquiry. The labour involved in sorting these cases was partly short-circuited through the good offices of Colonel W. d'A. Maycock, Commandant, Army Blood Supply Depot, who supplied a list of approximately 1,500 military patients with transfusion treatment in F.T.U.s during the Normandy campaign from June to November 1944. Details of the amount and nature of the transfusion (i.e. whole blood or plasma) were included. All cases were first checked through Record Offices to classify them as: (*a*) dead; (*b*) effectives; (*c*) discharged, with appropriate date. Case records of all men who were effective at the time of the inquiry (September 1945 onwards) and of discharged men were then examined in detail. Details of transfusions were checked and additional transfusions after evacuation to U.K. were noted. Cases without complete medical documents from admission to a medical unit until final discharge from hospital or convalescent depot were rejected. The case records of three classes of patient satisfactory for follow-up over a minimum period of six months after transfusion were examined for evidence of jaundice: (*a*) effectives; (*b*) discharged from the Army after more than 6 months' stay in hospital; (*c*) discharged from the Army after less than 6 months in hospital but more than 6 months after transfusion. The size of this residual sample was 462.

For the study of jaundice associated with treatment of syphilis the sample was made up of: (*a*) cases in the United Kingdom during 1943 and 1944; (*b*) a smaller group of overseas cases treated with penicillin in the latter part of 1944 alone. It will be convenient to present the results of the enquiry separately with respect to the three main treatments in use, viz. long-term arsenic (L.T.A.), short-term arsenic (S.T.A.), and penicillin (PEN). Cases treated with the first of these make up a large bulk of the total sample. Consequently, they supply the greater part of the evidence relevant to the issues investigated.

In any investigation of the statistics of disease it is necessary to examine the role of variables known to distort impressions gained from crude figures. An outstanding one is age. The incidence of so-called post-arsphenamine jaundice is much the same in all age-groups of the Army population of syphilitics. From the U.K. sample of this inquiry we get the following rates, none of which differs significantly from the overall value of $34{\cdot}4\% \pm 1{\cdot}1$.

Age	*% incidence*
18–20	$35{\cdot}2 \pm 4{\cdot}0$
21–25	$36{\cdot}1 \pm 2{\cdot}0$
26–30	$33{\cdot}5 \pm 2{\cdot}0$
31–35	$32{\cdot}6 \pm 2{\cdot}5$
36–40	$37{\cdot}9 \pm 3{\cdot}5$
Over 40	$29{\cdot}9 \pm 4{\cdot}1$

By contrast, infective hepatitis, like other communicable diseases which confer immunity, is relatively more common in the younger age groups. As elsewhere pointed out independently by McKinlay and Truelove (*ibid.*) and Hogben and Johnstone (1946), this contrast offers a powerful objection to the view that the virus of infective hepatitis is responsible for jaundice during treatment of syphilis.

3. Declining Incidence of Jaundice associated with Syphilis Treatment

The following figures based on 1,955 L.T.A. cases show that the percentage incidence of jaundice among L.T.A. cases underwent a spectacular decline foreshadowed in the second half of 1943; i.e. after introduction of new instructions (June 1943) with respect to sterilization of syringes.

January–June 1943	$45{\cdot}1 \pm 1{\cdot}9$
July–December 1943	$39{\cdot}8 \pm 1{\cdot}9$
January–June 1944	$20{\cdot}6 \pm 1{\cdot}8$
July–December 1944	$5{\cdot}4 \pm 2{\cdot}0$
Whole period 1943–44	$34{\cdot}4 \pm 1{\cdot}1$

Since the view which prompted the new regulations was already gaining ground by the middle of 1943, it is instructive to break down the L.T.A. sample by the individual centres at which patients started treatment (Tables I and II). The distribution of cases with respect to time of onset in Table III shows that about one-third of jaundice cases occurred before a patient could have started a second course of treatment; and since the data point to a long period of incubation, the infective hypothesis implies that the overwhelming majority of cases became infected before starting a second course in a centre other than the one at which they first received treatment. Table I shows that the level of incidence was universally though not uniformly high in the first half of 1943; and decline was conspicuously unequal thereafter.

In view of evidence with respect to the mean incubation period set out later, we may consider cases of jaundice occurring less than 150 days after beginning of treatment as due to infection in the *first* treatment centre. Table II, which refers only to such cases, emphasizes the two conclusions stated above. Comparable figures for S.T.A. cases are too few to be worthy of discussion in this context; but scrutiny of the penicillin cases discloses a noteworthy feature. These included a U.K. group of 290 and an overseas sample of 124. The incidence of jaundice among them (August 1944–February 1945) was as follows:

U.K.	$2{\cdot}0 \pm 0{\cdot}9$
Overseas	$20{\cdot}2 \pm 3{\cdot}6$

This striking difference with respect to the use of one and the same drug is not entirely unequivocal, since it may conceivably be at least in part attributable to the general health of the patients. None the less, it is entirely consistent with the view that jaundice in syphilitics under treatment can be propagated by insufficient care with respect to sterilization of instruments.

It seems clear that a fairly high proportion of the syphilitic population was

TABLE I

PERCENTAGE INCIDENCE OF JAUNDICE IN PATIENTS STARTING L.T.A. TREATMENT IN VARIOUS V.D. CENTRES AT DIFFERENT TIME-PERIODS; TOTAL INCIDENCE DURING TREATMENT

Time—period	Gartlock	Preston	Lincoln	Colchester	Harrow Rd.	Rl. Herbert, Woolwich	Connaught	R.V.H. Netley	Others
1943 January–June	44·7 ±7·3	54·9 ±5·5	44·7 ±8·1	48·8 ±7·6	36·5 ± 6·7	22·2 ±10·1	39·0 ± 6·3	35·9 ±6·0	48·2 ±3·0
July–December	28·0 ±7·0	33·7 ±4·8	44·6 ±6·2	48·8 ±8·0	51·3 ± 8·1	44·0 ±10·1	36·7 ± 6·9	28·6 ±7·0	41·8 ±3·2
1944 January–June	8·3 ±8·3	14·7 ±3·4	30·3 ±5·7	28·3 ±6·2	40·6 ± 8·8	20·0 ± 8·2	10·0 ±10·0	0·0	17·4 ±2·7
July–December	—	3·3 ±3·2	7·1 ±7·1	0·0	12·5 ±12·5	0·0	—	—	6·3 ±3·1
Whole period	33·3 ±4·7	29·7 ±2·6	36·6 ±3·6	39·7 ±4·0	40·5 ± 4·3	25·6 ± 4·8	35·6 ± 4·3	30·4 ±4·3	35·3 ±1·7

TABLE II

PERCENTAGE PATIENTS DEVELOPING JAUNDICE IN LESS THAN 150 DAYS AFTER STARTING L.T.A. TREATMENT AT VARIOUS V.D. CENTRES

	Gartlock	Preston	Lincoln	Colchester	Harrow Rd.	Rl. Herbert, Woolwich	Connaught	R.V.H. Netley	Others
1943	28·8 ±4·8	31·0 ±3·5	31·1 ±4·6	31·0 ±5·0	30·8 ±4·7	20·9 ±6·3	25·0 ±4·2	15·1 ±3·5	33·4 ±2·1
1944	8·3 ±8·3	6·5 ±2·1	18·7 ±4·4	12·3 ±4·3	27·5 ±7·1	2·9 ±2·8	0·0	0·0	9·5 ±1·8

TABLE III

PERCENTAGE DISTRIBUTION OF TIME OF ONSET

Date of initial treatment	Days from beginning of treatment												Total	No. of cases
	Under 46	46–75	76–105	106–135	136–165	166–195	196–225	226–255	256–285	286–315	316–345	Over 345		
1943 January–June ..	3·0	5·3	31·8	22·5	18·2	6·3	5·3	2·3	2·3	0·7	1·0	1·3	100·0	302
July–December	2·0	4·9	25·3	25·7	17·6	8·6	6·9	1·6	3·3	0·8	0·8	2·4	100·0	245
1944 January–June ..	1·9	2·9	27·9	24·0	15·4	11·5	4·8	2·9	1·0	4·8	0	2·9	100·0	104
July–December	14·3	0	0	28·6	14·3	14·3	0	14·3	14·3	0	0	0	100·0	7
Whole period	2·6	4·7	28·4	24·0	17·5	8·1	5·8	2·3	2·6	1·4	0·8	2·0	100·0	658

infected with the icterogenic agent during the peak period of incidence at the beginning of 1943. In such circumstances the probability of infection at an early stage of treatment was high, and this sufficiently explains the high concentration of cases whose time of onset was in the zone between 75 and 135 days from the beginning of the first course. By the same token we might expect to find a much greater spread towards the upper limit of the time of onset as the gross incidence of jaundice declined with concomitant proportionate reduction of carriers. That this is not so calls for explanation. Indeed, the figures in Table III suggest that susceptibility to the infective agent is maximal at the *beginning* of treatment, being thus dependent on the syphilitic process.

The high incidence of jaundice among syphilitics at the beginning of 1943 is in striking contrast to the known incidence of jaundice among patients simultaneously treated with pooled homologous sera. Evidence from this source indicates that the proportion of persons who react by delayed jaundice to transfusion with blood obtained from large pool of donors is not high, being about 5%. This is not what the high figures for jaundiced syphilitics at the beginning of 1943 might lead us to suppose, if we accept the hypothesis that such jaundice is in fact determined by an agent spread by syringes contaminated with blood of infected individuals. Among others, two explanations for the anomaly suggest themselves:

(*a*) that the procedure of Army venereal disease clinics before 1943 constituted a selective machinery for the build up of a population isolate with an inordinately high proportion of infected donors and/or a stock of instruments more or less permanently contaminated with the icteric agent;

(*b*) that circumstances peculiar to the treatment of syphilis and/or to the syphilitic process itself favour high susceptibility to such blood-borne infective agents as may evoke icterus in appropriate circumstances.

The second issue is the theme of the section which follows.

4. Significance of Arsenicals and of the Syphilitic Process

The hypothesis that an infective agent is a *necessary* condition for development of jaundice does not necessarily imply that it is also a *sufficient* one. How far the nature and quantity of the drug and how far the syphilitic process are respectively among contributory circumstances propitious to icteric manifestations are issues which we can disentangle only by a simultaneous breakdown of our data with respect to both. In comparing results of different therapies we shall therefore split our cases with respect to the stage of disease when treatment began. Needless to say, valid interpretation of data bearing on either of the issues involved presupposes due consideration of the distribution of cases by date of starting treatment; but it would be unduly prolix to present all the ensuing data separately for comparable periods. It must suffice to say that such data with respect to long-term arsenotherapy throughout the whole period, as appear in Table IV, point to conclusions consistent with data classified separately for three-monthly periods. Similar remarks apply *mutatis mutandis* to other comparisons below, unless there is a

statement to the contrary. Table IV exhibits no statistically significant differences with respect to the incidence of jaundice among patients respectively receiving long-term neoarsphenamine and mapharside at the same stage of the disease when treatment started. Rates for patients receiving short-term arsenotherapy and penicillin are not comparable, since these treatments came into use only at the end of the period to which Table IV refers.

TABLE IV

PERCENTAGE INCIDENCE OF JAUNDICE IN RELATION TO NATURE OF ARSENICAL DRUG EMPLOYED FOR FIRST COURSE AND STAGE OF SYPHILIS AT WHICH TREATMENT BEGAN

Stage of disease	N.A.B. (1,010 cases)	Mapharside (209 cases)
Primary Unspecified	44·9 ±6·0	35·7 ±13·3
Primary Sero-negative	35·4 ±2·9	34·7 ± 6·8
Primary Sero-positive	39·6 ±2·5	44·7 ± 5·4
Secondary ..	36·9 ±2·6	36·1 ± 6·1

During the period under review there was a striking contrast between the liability of syphilis patients to jaundice and to indisputably toxic effects of arsenicals *per se*. The following figures based on the L.T.A. sample of this enquiry show that rates for arsenical dermatitis, by far the most common complication of arsenotherapy other than hepatitis, remained constant while the incidence of jaundice underwent a spectacular decline.

	% *Jaundice*	% *Dermatitis*
January–June 1943	45·1 ±1·9	6·6 ±3·0
July–December 1943	39·8 ±1·9	6·2 ±3·0
January–June 1944	20·6 ±1·8	7·5 ±3·6
July–December 1944	5·4 ±2·0	8·5 ±7·7

The data set forth above and rates for penicillin treatment cited earlier provide no grounds for believing that one or other form of arsenic treatment is more or less

TABLE V

PERCENTAGE INCIDENCE OF JAUNDICE RELATED TO STAGE OF SYPHILIS AT WHICH TREATMENT BEGAN

Time—period	Primary unspecified	Primary sero-negative	Primary sero-positive	Secondary	No clinical sero-positive	All stages
1943:						
January–June ..	41·1 ±6·6	44·1 ±3·8	52·0 ±3·1	36·8 ±3·5	57·1 ±11·6	45·1 ±1·9
July–December ..	50·0 ±6·6	40·6 ±3·8	40·7 ±3·1	33·1 ±4·0	28·6 ±12·5	39·6 ±1·9
1944:						
January–June ..	22·0 ±5·8	20·8 ±3·6	24·0 ±3·5	15·3 ±2·9	33·3 ±11·4	20·6 ±1·8
July–December ..	0·0	5·9 ±4·0	9·8 ±4·1	0·0	0·0	5·5 ±2·0
Whole period ..	37·7 ±3·7	34·1 ±2·1	38·9 ±1·8	27·0 ±1·9	37·3 ± 6·3	34·3 ±1·1

propitious to overt jaundice in the absence of adequate precautions against syringe contamination, nor any reason to suppose that arsenotherapy is more risky than penicillin if precautions are in fact adequate.

We have now to ask whether the syphilitic process as such plays a significant contributory role. In this context the syphilitic process signifies any relevant conditions arising from the disease itself. Table V brings out a striking difference which suggests an affirmative answer to the question stated last. The contrast is more explicit if we condense information therein with respect to jaundice rates as follows:

	Primary stage	*Secondary stage*	*All stages*
January–June 1943	48·0 ±2·3	36·8 ±3·5	45·1 ±1·9
July–December 1943	41·8 ±2·3	33·1 ±4·0	39·6 ±1·9
January–July 1944	19·4 ±1·9	12·6 ±2·4	17·5 ±1·5

We have here definite evidence for the view that the syphilitic process does play a significant contributory role in the phenomenon under discussion. For reasons already stated, this receives some support from the trend of rates shown in Table III. It is also sustained by the appreciable incidence of jaundice among syphilitic patients treated with penicillin, a drug which is not of itself an agency contributory to jaundice. Among 296 cases of gonorrhoea treated with intramuscular penicillin in U.K. clinics from July 1944 to September 1945 no single individual had developed jaundice by the end of 1945. From another enquiry undertaken in the Directorate of Medical Statistics at the War Office by Dr. Hunt, we have other evidence for the view that penicillin does not increase liability to jaundice. Examination of cases of jaundice among battle casualties treated with or without systemic penicillin discloses the following rates:

With transfusion and systemic penicillin (B.L.A.) ..	4·3 ±0·8
Ditto without systemic penicillin (C.M.F.)	4·2 ±1·7
Without transfusion with systemic penicillin (B.L.A.) ..	0·35 ±0·1
Ditto without systemic penicillin (C.M.F.)	0·89 ±0·4

5. Delayed Jaundice associated with Blood Transfusion

Although penicillin, *per se*, exerts no influence on liability to jaundice, evidence set forth above shows that blood transfusion is commonly associated with increased liability. Before proceeding to the exposition of other data bearing more directly on the nature of the agent or agents respectively responsible for jaundice associated with treatment of syphilis and delayed jaundice following blood transfusion, it is appropriate to draw attention to an important difference between rates for delayed jaundice among two classes of casualties which received transfusion, viz. those who received *whole* blood only and those who received plasma. The following figures show that plasma as used for these cases is more icterogenic than whole blood.

	No. of patients	*% developing jaundice*	*Difference*
Whole blood only	248	0·81 ±0·32	4·33 ±1·61
Plasma alone or with blood	214	5·14 ±2·28	

A sufficient explanation of this difference is that:

(*a*) one bottle of whole blood comes from a single donor;

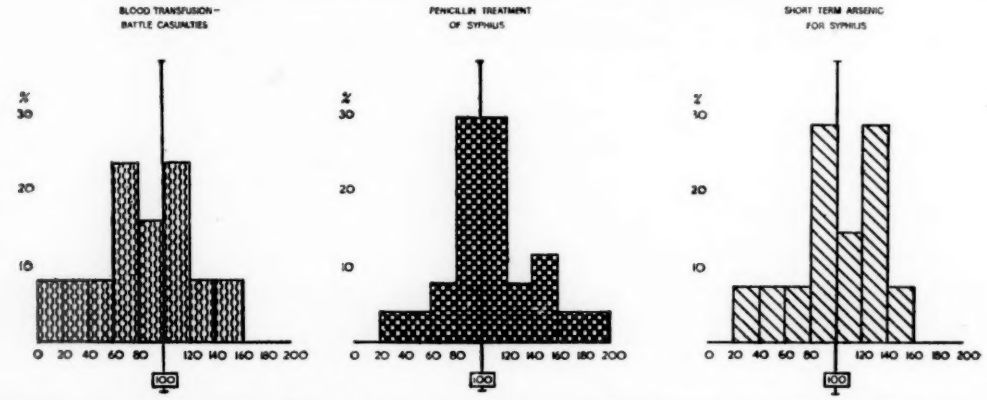
(*b*) one bottle of plasma comes from a pool to which many donors contribute.

Whereas a bottle of whole blood can carry an icterogenic agent from only one donor, a bottle of pooled plasma may indeed contain an icterogenic agent from any one of about 500 donors.

6. The Incubation Period of the Several Types of Jaundice

The table on p. 28 showing concomitant incidence of such other communicable diseases as occurred in a highly heterogeneous syphilitic population with a high

SERUM HEPATITIS—INCUBATION PERIOD (DAYS)



incidence of hepatitis shows that the putative infective agent of so-called post-arsphenamine jaundice *either* stays longer in the blood stream *or* is vastly more resistant to sterilization procedures than the agent of any common communicable disease. If it is infective hepatitis, the virus of infective hepatitis must itself be very different in one or both ways from other viruses; but it is more probable that the jaundice in syphilis is evoked by an infective agent which is *not* the virus of infective hepatitis. One reason for believing so, and one sufficiently striking of itself, depends on its age distribution already mentioned on p. 20. The figures there shown refer to L.T.A. and the overseas penicillin sample is confirmatory in so far as rates for the age groups up to and over 25 are respectively $20{\cdot}0 \pm 6{\cdot}4$ and $19{\cdot}5 \pm 4{\cdot}4$. For reasons set forth by Hogben and Johnstone (1946) this suggests that the putative infective agent of post-arsphenamine jaundice does not evoke appreciable immunity to subsequent infection, as does the virus of infective hepatitis. It is therefore instructive to seek further information concerning the prophylactic effect of a previous attack of infective hepatitis. Our records provided only 10 cases of syphilitics with a previous history of the disease. Of these, 2 had jaundice during treatment in V.D. clinic. The incidence $20{\cdot}0 \pm 13{\cdot}3$ does not significantly differ from the overall figure $34{\cdot}5 \pm 1{\cdot}1$ for the same period. Of itself this signifies little, but is consistent with evidence of a field enquiry undertaken by McKinlay and Truelove (ibid.) in Italy where infective hepatitis was more prevalent. Their

corresponding figures for 35 and 837 cases respectively with and without previous history of infective hepatitis were $34 \cdot 3 \pm 8 \cdot 1$ and $36 \cdot 3 \pm 1 \cdot 7$.

TABLE VI

TIME OF ONSET OF JAUNDICE IN RELATION TO STAGE OF DISEASE AT WHICH TREATMENT BEGAN (L.T.A. SERIES)

Stage of Disease	Days after beginning of treatment												Total	No. of cases
	Under 46	46–75	76–105	106–135	136–165	166–195	196–225	226–255	256–285	286–315	316–345	Over 345		
Primary unspecified	1·6	6·5	27·4	29·0	11·3	8·1	3·2	1·6	4·8	—	—	6·5	100·0	62
Primary negative ..	1·8	6·7	30·0	24·5	17·2	6·1	4·9	3·1	2·5	1·2	1·2	0·6	100·0	163
Primary positive ..	2·2	3·0	26·9	21·3	20·5	9·3	6·0	2·2	3·4	2·2	0·7	2·2	100·0	268
Secondary	4·1	4·9	28·7	27·0	14·8	8·2	9·0	2·5	—	—	0·8	0·0	100·0	122
Sero + ...	5·3	5·3	36·8	18·4	15·8	7·9	2·6	—	—	2·6	—	5·3	100·0	38

TABLE VII

RELATION OF AGE TO THE TIME OF ONSET OF JAUNDICE

Age	Days after starting treatment												Total	No. of cases
	Under 46	46–75	76–105	106–135	136–165	166–195	196–225	226–255	256–285	286–315	316–345	Over 345		
18–25	2·3	5·5	29·7	25·8	16·0	7·8	5·1	2·3	2·0	0·8	0·8	2·0	100·0	256
26–30	2·2	3·9	26·3	26·8	18·4	7·8	3·9	2·8	2·8	2·8	0·6	1·7	100·0	179
31–35	3·4	3·4	28·4	24·1	19·0	9·5	6·9	0·9	0·9	0·9	1·7	0·9	100·0	116
36 + ..	2·8	5·6	29·0	15·0	17·8	7·5	9·3	2·8	5·6	0·9	—	3·7	100·0	107

An issue with respect to which our data provide a basis for more satisfactory comparison between the several types of jaundice is the period of incubation. Table III sets forth the case distribution for L.T.A. patients by time of onset from start of treatment. Neither the stage of the disease at start of L.T.A. treatment (Table VI) nor the age of the patient (Table VII) appear to affect the time of onset. The data suggest a mean period of incubation long in comparison with infective hepatitis, but do not of themselves entitle us to set clear-cut limits to it. More precise information is obtainable by recourse to corresponding data pertaining to patients treated by *intensive* methods, i.e. S.T.A. and PEN. Table VIII sets out data with respect to a six months' follow-up of such cases with corresponding data for transfusion jaundice (Tr.J).

Although the figures are small they consistently point to a mean period of incubation in the neighbourhood of 100 days. We have to bear in mind that they are not strictly comparable in so far as the date of exposure to the putative infective agent is defined within limits of 1 day for Tr.J cases, 9 days for PEN, and 20 days for S.T.A. The real incubation period for any case may fall short of the date of onset from start of treatment by these numbers. The incubation period of infective hepatitis is in the range 20–40 days. For what we may here collectively call serum hepatitis about 75% of cases occur 80 days *or more* after exposure and 50% occur within the range 80–120 days. Allowance for the margin of error in fixing the exact

TABLE VIII
INCUBATION PERIOD

DAYS FROM BEGINNING OF TREATMENT

	0–19	20–39	40–59	60–79	80–99	100–119	120–139	140–159	160–179	180–199	Total	No. of cases
S.T.A.	0	7·1	7·1	7·1	28·6	14·3	28·6	7·1	0	0	100·0	14
PEN	0	3·7	3·7	7·4	29·6	29·6	7·4	11·1	3·7	3·7	100·0	27
Tr.J	7·7	7·7	7·7	23·1	15·4	23·1	6·6	7·7	0	0	100·0	13

PERCENTAGE CASES BY DATE OF ONSET

	Under 40 days	40–79 days	80–119 days	120–159 days	160 and over	Total
S.T.A.	7·1	14·2	42·9	35·7	0	100·0
PEN	3·7	11·1	59·2	18·5	7·4	100·0
Tr.J	15·4	30·8	38·5	15·4	0	100·0
All	7·5	16·7	50·0	22·2	3·7	100·0

date of exposure does not materially distort these estimates. The contrast is all the more remarkable if we pay regard to the two modes of transmission. If infective and serum hepatitis are attributable to the same virus, there is *prima facie* reason to expect that the incubation period of the former would be longer, since the infective agent has to penetrate the site of the infection before it can establish itself elsewhere.

7. NATURE OF THE ICTEROGENIC AGENT OF SERUM HEPATITIS

The assumption that a venereal disease clinic constitutes a population isolate *sui generis* in virtue of procedure favourable to the spread of a putative infective agent of jaundice implies the existence within such a population isolate of a high incidence of any communicable disease which can be transmitted through blood as a medium. It is therefore pertinent to ask what was the incidence of known communicable, more especially virus, diseases in the syphilitic population, when the incidence of jaundice putatively attributable to a syringe-spread infection was at its peak level in the neighbourhood of 45%. The ensuing table, which shows actual numbers of cases among Army syphilitics—U.K. 1943–44—supplies a sufficient answer and is particularly suggestive in so far as it lists diseases, e.g. rubella, which are certainly as common as infective hepatitis in the Army population.

	Total population of syphilitics	*Jaundice*	*Rubella*	*Chicken-pox*	*Glandular fever*	*Herpes facialis*	*Herpes zoster*	*Pneumonia (all forms)*
1943	1,320	562	2	1	1	2	1	2
1944	635	111	0	0	0	2	0	1
Total	1,955	673	2	1	1	4	1	3

When we have to decide whether two clinical conditions are attributable to one and the same agent, we do well to remember that a single clear-cut difference overrides the value of any number of striking similarities. The collective weight of evidence set forth above therefore tells heavily against the view that the virus of infective hepatitis is responsible for *serum* (including so-called post-arsphenamine) jaundice. If so, we are faced with a nexus of new problems involving not merely the identification of the icterogenic agent itself but also its method of propagation.

That the icterogenic agent is a virus receives strong support from several circumstances: its heat lability, its delayed action, and the minute quantities of blood which can convey it. These circumstances, in themselves highly suggestive, are not wholly conclusive. They are indeed consistent with the assumption that the icterogenic agent is a heat-labile by-product of the normal metabolism of certain individuals capable of slow pathogenic action in other individuals. The relevant distinction implicit in the usual connotation of the term virus is whether or not the agent is capable of *growth*. In practice, this signifies that we can dilute it indefinitely and recover from a minute fraction of the original source a quantity equivalent to what was originally present in the source itself. In the absence of methods of assay *in vitro* the only way of reaching a decisive conclusion about this is to test whether it retains its efficacy after transmission through a chain of test subjects successively inoculated with minimal quantities of sera or whole blood. By recourse to this method, Paul *et al.* (1945) have obtained highly suggestive indications in favour of the view that the icterogenic agent of serum hepatitis is amenable to indefinite dilution.

It is clearly important to seek such indications preferably by recourse to a suitable test animal if such can be found, alternatively by experiments on human volunteers willing to submit to a procedure with attendant risks that are by no means trivial. Meanwhile, it is not unprofitable to examine the implications of the assumption that the agent of delayed serum hepatitis is in fact a virus. Within the framework of this provisional assumption we have to meet the challenge of three conclusions suggested by our enquiry:

(i) there exists a small but not inconsiderable group of persons who are carriers of the icterogenic agent;

(ii) a high proportion of persons—perhaps as many as 50%—are resistant to its effects when introduced into the circulation;

(iii) its introduction into the circulation of individuals does not appear to confer immunity to subsequent inoculation.

The last of these three conclusions is least firmly established and further examination of its consequences *vis à vis* the foregoing assumption will make clear the importance of establishing it firmly or discrediting its validity. The assertion that the virus of infective hepatitis is *not* the icterogenic agent of delayed serum hepatitis implies that infective hepatitis as a disease endemic or epidemic in a normal population is a *singular* clinical entity. This assumption is not beyond

dispute, but its provisional acceptance is worth while, if only because the inescapable result of accepting it emphasizes the need for further assurance. If we do accept it, we are driven to the conclusion that delayed serum hepatitis is a disease of which the only known vector is the physician and the only known organ by which the vector can transmit the infective agent is the syringe.

Within the compass of the preceding assumptions, which admittedly call for more rigorous validification, we are thus led to ask by what means the putative virus can persist endemic within a population not exposed to *artificial* methods of transmission. It may be that further research will reveal possibilities other than such as existing information suggests. The possibility that viruses may arise *de novo* in the living body is repugnant to current teaching; and if it is not necessarily inconceivable in the light of the most recent research on their nature it would assuredly be over-bold to reopen the discussion of spontaneous generation without exploring an alternative which comes within the province of available experience and has more to commend it on other grounds. Among plants we have long been familiar with viruses which maintain their existence within a population by transmission through successive generations of individuals, each affected parent being a vector for its own offspring. The infective agents of the so-called mosaic diseases have indeed three characteristics which are at least suggestive in this context: (*a*) they require no vector nor any such external medium of propagation as droplet or faecal infection imply; (*b*) they confer no immunity by their presence; (*c*) the effects of their presence, though manifest, may be entirely innocuous, as is true of the mosaic virus of variegated tulips.

To be sure, propagation of this sort commonly goes with vegetative reproduction of the plant host; but the viruses of bean mosaic and lettuce mosaic are conveyed by the *ovule*. Hence there is nothing to exclude the possibility that human transmission could be accomplished through the medium of sexual generation *via* either one or both of the gametes, by transplacental spread to the foetus or by lactation. In this context it would be premature to advocate any such a hypothesis of parental transmission without further examination of issues which remain dubious and of alternatives which may suggest themselves in the light of new data. Meanwhile such speculations are not fruitless, if they focus attention more sharply on the needs to elucidate three issues: (*a*) whether the icterogenic agent of serum hepatitis is in fact a virus; (*b*) whether cases of an identical nature do in fact occur in the absence of artificial means of propagating a blood-borne infection; (*c*) what fraction of a normal population are carriers of an icterogenic agent.

8. Practical Implications

Data presented earlier in this communication suggest not only theoretical issues for further research but positive guidance for the practice of preventive medicine. It is convenient to consider these separately with respect to jaundice associated with syphilis therapy and with blood transfusion.

(*a*) Evidence here presented confirms the view that the majority of cases of

jaundice associated with syphilis therapy are the result of an icterogenic agent transferred from patient to patient through the medium of imperfectly sterilized syringes. When sterilization procedures are inadequate in venereal disease clinics a very high proportion (50%) of syphilis patients may develop jaundice as a result of their peculiar liability to this condition. Sterilization by boiling reduces the incidence of jaundice to trivial proportions. In view of the high incidence of jaundice associated with one series of penicillin-treated cases, it is apparent that a high standard of sterilization procedure should be maintained irrespective of the therapeutic agent employed. Indeed, the chemical nature of the therapeutic agents in the doses commonly used seems to be of negligible importance.

(*b*) In view of the widespread use of blood transfusion as a therapeutic measure, it is important to evaluate the magnitude of the risk of jaundice following transfusion. Evidence presented in Section 5 yields a clear-cut answer. When blood comes from single donors, transfusion carries a negligible risk of subsequent delayed jaundice. On the other hand, use of plasma from large pools of blood obtained from many donors makes the risk of delayed jaundice by no means negligible (5% in this series).

These findings are consonant with the experience of Loutit and Maunsell (1945) who found that no cases of jaundice occurred among subjects inoculated with plasma obtained from 96 single donors. It thus seems clear that the use of blood or blood products obtained from large pools should be abandoned in civilian medical practice. On the other hand stable blood products may be needed on a vast scale under conditions of active warfare, when the risk of jaundice may be of small account by comparison with the advantages of mass production from large pools of blood. To what extent large-scale production from pools of a few donors only is then practicable is an issue to be decided with due regard to considerations relevant to methods of manufacture.

9. Summary

1. Of syphilis patients starting long-term arsenic treatment in military V.D. centres in U.K. during the first half of 1943, approximately half developed jaundice during treatment. Following introduction of improved sterilization procedures, incidence of jaundice underwent a spectacular decline, until it was about 5% in the second half of 1944. This confirms the view that the majority of cases of jaundice associated with treatment of syphilis are due to a syringe-spread heat-labile icterogenic agent.

2. Different arsenicals are associated with similar incidence of jaundice during treatment. During the treatment when incidence of jaundice was sharply declining, incidence of arsenical dermatitis remained steady. Under propitious circumstances, penicillin treatment is also attended by high incidence of jaundice. In doses commonly employed, arsenicals therefore seem to exert little or no influence on liability to jaundice.

3. On the other hand, the syphilitic process seems to increase susceptibility to jaundice, susceptibility being greatest during the very early stages of syphilis.

4. Transfusion with blood obtained from single donors carries a negligible risk of subsequent delayed jaundice. Transfusion of blood or blood products obtained from large pools carries a significantly higher risk of subsequent jaundice (about 5% in this series).

5. Although subject to great variation the most common incubation period of serum hepatitis, both among syphilitic patients and Army patients who receive blood transfusion, is in the region of 100 days. This is much more protracted than the incubation period of infective hepatitis (21–40 days).

6. During the period of high incidence of jaundice, the incidence of other communicable diseases in the syphilitic population was negligible. Whereas infective hepatitis is relatively more common among the youngest Army age groups, age has little or no influence on liability to jaundice among syphilitics. These findings converge with other evidence to the conclusion that the virus of infective hepatitis is *not* the icterogenic agent responsible for jaundice among syphilitics.

7. The theoretical implications of the view that serum hepatitis is due to a virus which is not that of infective hepatitis are challenging in so far as they prompt the question: By what means does the virus persist endemic in the population? A possible interpretation is the subject of discussion in Section 7.

8. Two important practical implications emerge from this study:

(*a*) because syphilitics are unduly liable to jaundice, a high standard of sterility must be maintained during their treatment, irrespective of what therapeutic agents are employed;

(*b*) the use of blood or blood products obtained from large pools should be abandoned in civilian medical practice, though their use may still be justifiable under the special conditions of active warfare.*

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* Since this article went to press, the *British Medical Journal* (September 21st, 1946, p. 409) has published one by Spurling, Shone, and Vaughan, who have independently established by more extensive observations the conclusion that blood transfusion with pooled serum or plasma is associated with a much higher risk of serum hepatitis than is transfusion with whole blood from individual donors.

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EPIDEMIOLOGY OF INFECTIVE HEPATITIS AMONG ALLIED TROOPS IN ITALY

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For infective hepatitis we have not, as for most other important diseases, an extensive peace-time background of knowledge as a directive to the most profitable lines of study. The aim of this field inquiry among troops in Italy has been to obtain accurate knowledge of the influence of such circumstances as: (*a*) age; (*b*) previous attacks; (*c*) length of service in areas of high prevalence; (*d*) other agencies such as methods of feeding, sanitation, and overcrowding.

A problem with so many variables worthy of investigation ideally demands the simplest epidemiological set-up available. This implies a static or semi-static population, for which the following information is accessible: (i) relevant particulars (e.g., age, length of service, rank) of all individuals in the group, including immigrants and emigrants; (ii) dates of entrance and exit of members of the group; (iii) particulars of intragroup differences with respect to external circumstances or habit of life.

Prima facie, base units would commend themselves for study with these considerations in view; and experience of the previous year, when infective hepatitis was prevalent in base as in forward units, encouraged us to undertake extensive preparations to provide background data from base units in the area. Low incidence of the disease frustrated this plan. Accordingly, it was necessary to concentrate attention on forward troops. We therefore chose New Zealand and Canadian units, because they were subject to massive epidemics at the time. Inescapably, therefore, the inquiry was beset by difficulties arising from rapidly fluctuating location and population structure of the social group.

In its preliminary stages the need for two classes of information not mentioned hitherto became evident: (*a*) prevalence of infective hepatitis in the indigenous population, especially in view of reports to the effect that Italian troops had suffered heavily from the disease in the Western Desert; (*b*) concomitant features of jaundice among syphilitics undergoing arsenical treatment, especially in view of emergent indications of its infective nature and of its spread by contaminated syringes.

Infective Hepatitis among New Zealand Troops

For New Zealand troops available information relevant to our aim refers only to hospital admissions. In conformity with N.Z. Army medical regulations in force, these included all cases diagnosed as infective hepatitis, some being subicteric. Table I, which refers to 2nd N.Z.E.F., cites relative admission rates to hospital for the period mid-1942 to the end of 1944, and indicates the importance of infective hepatitis as a major problem of war medicine. Since infective hepatitis causes prolonged incapacity, such admission rates do not exaggerate its contribution to total wastage.

TABLE I

Showing the Relative Importance of Infective Hepatitis and Certain Selected Causes of Hospital Admission (2 N.Z.E.F.)

	Infective Hepatitis	Malaria	Enteric	Dysentery	Diarrhoea	V.D.	Battle Casualties	Accidents
1942 Jul.– ..	1·48	3·79	0·04	6·26	7·47	1·35	17·95	6·88
„ Oct.– ..	21·92	1·71	0·12	3·59	2·43	2·05	16·71	7·07
1943 Jan.– ..	2·80	1·39	0·07	2·28	1·78	1·94	11·33	13·07
„ Apr.– ..	1·06	1·65	0·02	5·67	4·68	2·06	12·89	12·60
„ Jul.– ..	1·72	1·86	0·97	11·76	4·73	1·91	0·00	11·63
„ Oct.– ..	3·20	1·98	0·95	4·94	3·70	1·64	15·28	15·75
1944 Jan.– ..	6·15	0·26	0·07	1·20	2·67	2·16	16·28	13·17
„ Apr.– ..	2·48	0·41	0·19	4·18	4·11	5·38	8·45	12·80
„ Jul.– ..	11·15	2·04	0·15	3·26	5·48	3·80	14·35	10·19
„ Oct.–Dec. ..	14·55	0·53	0·07	1·96	3·03	3·45	11·15	9·36
Jul., 1942–Dec., 1944	7·19	1·73	0·24	4·57	4·28	2·54	13·01	10·63

The New Zealand data have three advantages for our purpose: (i) the Expeditionary Force maintained in the field an admirable system of medical documentation covering all admissions to medical units; (ii) the troops were made up of reinforcement groups that had arrived in the Mediterranean zone at widely separated times, precise details of which were available: hence length of service in the zone was known for each reinforcement group; (iii) during a rest period in the middle of the epidemic the division chosen was able to carry out a complete census of rank, age, unit and reinforcement group.

Fig. 1 discloses the seasonal picture, which conforms to general experience—i.e., that epidemics of infective hepatitis occur in autumn and winter. The regularity of the configuration there shown conceals differences regarding the magnitude and timing of epidemic peaks in individual units within the total force. Comparison of the experience of individual units yielded no evidence that the

magnitude of an epidemic is closely associated with time of occurrence. Table II shows the date of onset of the median case in each divisional group during the

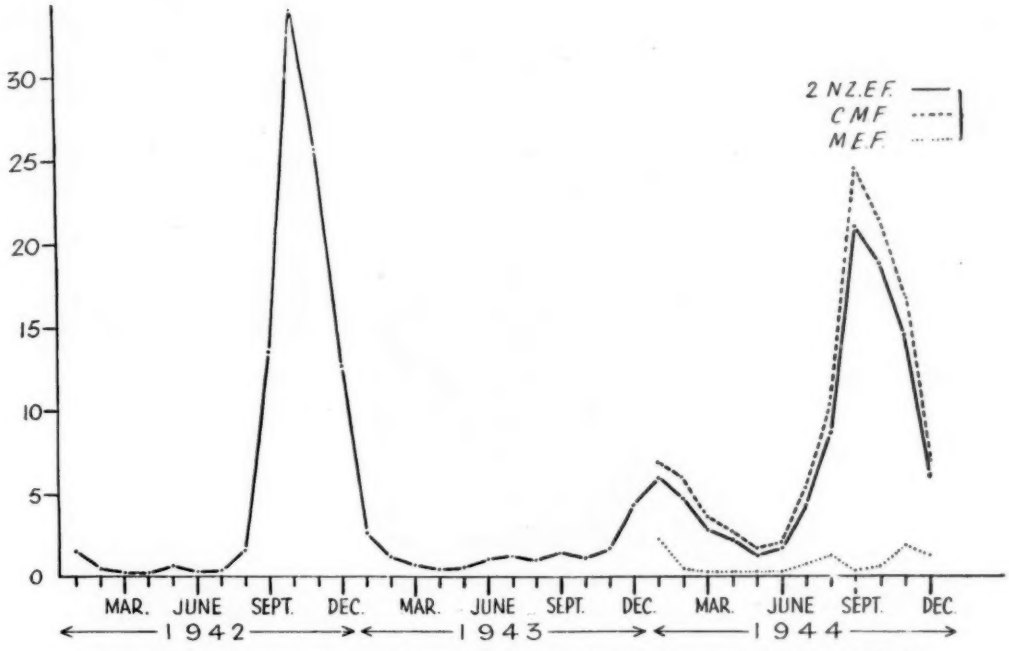

FIG. 1.—Crude rates per 1,000 population (2 N.Z.E.F.) monthly for 1942–44.

full epidemic of 1944, together with corresponding dates for upper and lower quartiles. The semi-interquartile range (extreme right-hand column) may be taken as an index of the total duration of a group epidemic.

TABLE II

SHOWING QUARTILE VALUES FOR DIVISIONAL GROUPS (2 N.Z. DIV.)

	Median	Lower Quartile	Upper Quartile	$\frac{Q_3-Q_1}{2}$
Infantry	23/ 9/44	29/8/44	20/10/44	26·0
Armoured	17/10/44	19/9/44	14/11/44	28·0
Engineers	29/ 9/44	9/9/44	18/10/44	19·5
Artillery	9/10/44	14/9/44	8/11/44	27·5
Medical	21/ 9/44	29/8/44	10/10/44	21·0
Workshops	29/ 9/44	29/8/44	2/11/44	32·5
H.Q.s	25/ 9/44	31/8/44	23/10/44	26·5
A.S.C.	14/10/44	19/9/44	17/11/44	29·5
Remainder	5/10/44	8/9/44	8/11/44	30·5
Total	31/ 9/44	7/9/44	31/10/44	27·0

Over the entire period of the 1944 epidemic the proportional incidence in each of four main age groups (20–24, 25–29, 30–34, and over 35 years) remained constant

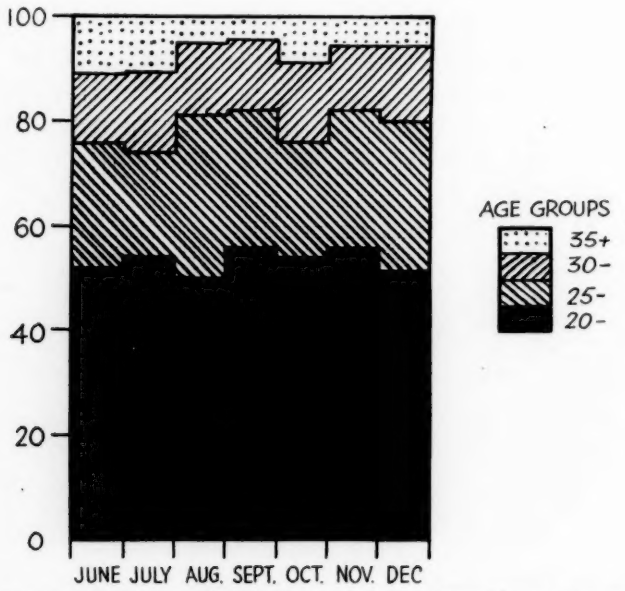

FIG. 2.—Proportional age-distribution of cases throughout the epidemic.

(Fig. 2). Fig. 3 shows the experience of three main *reinforcement* classes: (i) Groups 7 and under had arrived in the theatre before the major epidemic of 1942; (ii) Group

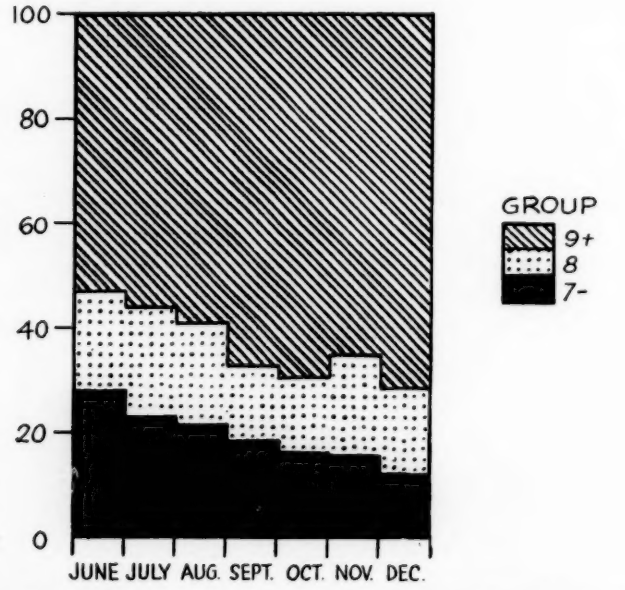

FIG. 3.—Proportional distribution of reinforcement groups throughout the epidemic.

8 arrived after the end of the 1942 epidemic and had been exposed to the minor winter epidemic of 1943–4, with its peak in January; (iii) Group 9 arrived after both epidemics referred to above, and had therefore no previous experience of large-scale exposure to infection.

We are thus in a position to record a human group situation comparable to an artificial set-up of Greenwood, Topley, and their collaborators (1936) in laboratory observations on mouse epidemics. They found that the newest immigrants to an infected herd were most susceptible at the beginning of an epidemic. The data exhibited in Fig. 3 show that the earliest reinforcement group makes its highest proportionate contribution to total incidence at the beginning of the major epidemic of late 1944. Thereafter its proportionate contribution consistently declines. The newest immigrant group exhibits a reverse trend—i.e., increasing proportionate contribution to total incidence as the epidemic spreads and declines.

This feature of the major epidemic of 1944 prompts a comparison of incidence in the three main reinforcement groups; but differences with respect to the age structure of the groups themselves call for an assessment of liability to infection at different ages as a necessary preliminary to valid comparison. Happily, available data make it possible to relate incidence to the population at risk in different age groups, and hence to estimate age-specific rates as a basis for standardization in what follows.

TABLE III

AGE-SPECIFIC RATES (1944 MAJOR EPIDEMIC)

Age	Population	Cases	Specific Rate (%)
Under 22	793	200	25·2
22	2,113	420	19·9
23	1,870	301	16·1
24	1,697	224	13·2
25–29	5,661	530	9·4
30–34	3,538	281	7·9
35–39	1,864	111	6·0
Over 39	550	26	4·7
Total	18,086	2,093	11·6

The relation between incidence and age shown in Table III tallies closely with the distribution given by Hogben and Johnstone (1945). Table IV shows corresponding specific rates of four major age groups separately for the three main reinforcement groups.

TABLE IV

AGE-SPECIFIC RATES BY LENGTH OF SERVICE IN THE MEDITERRANEAN ZONE

Age	Incidence %		
	Group 1–7	Group 8	Group 9 and over
20–24	14·2	14·2	18·9
25–29	5·9	10·3	15·1
30–34	5·1	6·8	11·7
35–39	3·6	4·9	8·3
40	2·5	5·3	7·5

With these data at our disposal we can compute age-standardized rates separately for the three main reinforcement groups as in Table V and Fig. 4.

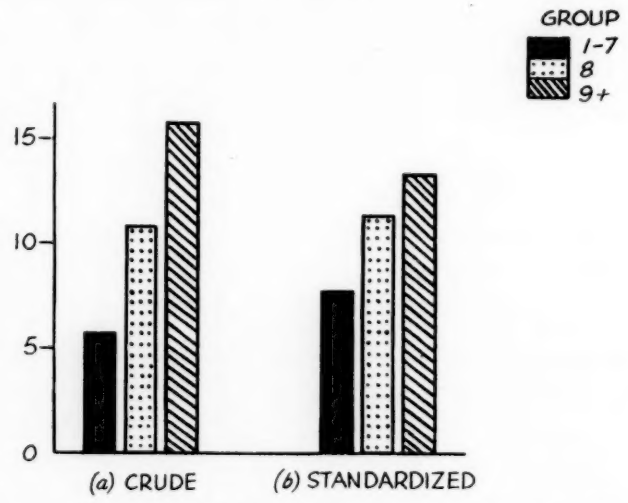

FIG. 4.—Incidence rates in the three reinforcement groups. (*a*) Crude. (*b*) Age-standardized.

TABLE V

INCIDENCE IN MAIN REINFORCEMENT GROUPS

	Rate per cent.		Relative to Groups 1–7	
	Crude	Standardized	Crude	Standardized
Groups 1–7	5·67	7·66	100	100
Group 8	10·87	11·22	190	146
Group 9+	15·79	13·31	278	174

Since the newest arrivals included a higher proportion of younger personnel, age standardization reduces differences with regard to incidence in the three groups, but standardized and crude rates in Table V tally in so far as they show that the groups most exposed to previous infection had the lowest and the group least exposed to previous infection had the highest infection in the major epidemic of 1944. Of itself this furnishes evidence for the view that an attack of infective hepatitis confers an appreciable measure of immunity. This conclusion receives additional support from the age distribution shown in Table III, for reasons discussed at length by Hogben and Johnstone (op. cit.). On the other hand, the difference exhibited in Table IV offers no evident clue to the phenomenon disclosed in Fig. 3.

It is thus clear that we have to undertake any comparison between units or intradivisional groups with due regard both to age and to length of service in an overseas theatre where the disease is prevalent. We may use the data in Table IV as a basis for computing appropriate correction factors for the crude rates of

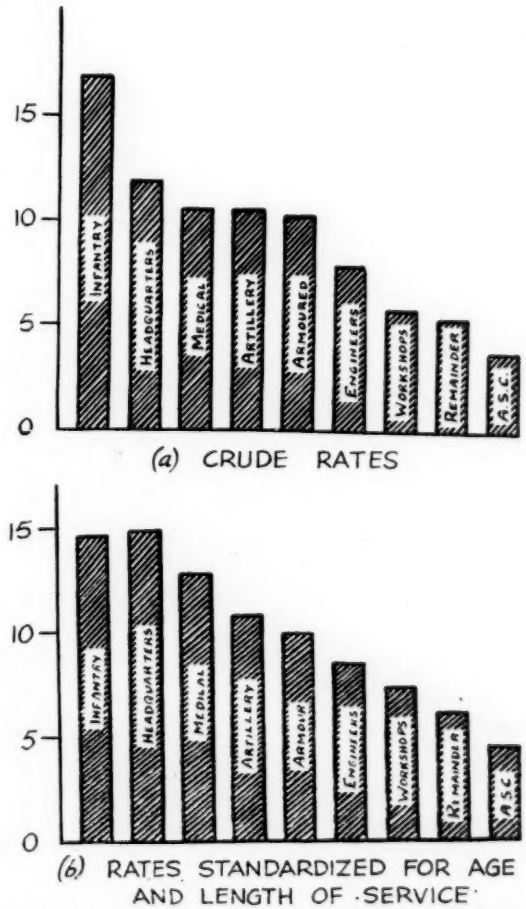

FIG. 5.—Incidence rates in Divisional groups.

incidence in different arms of the service as shown in Table VI. Such corrections do not greatly modify the picture which emerges from the crude rates themselves. Fig. 5 exhibits such differentials in respect of arm of Service; but we are unable to point to circumstances or habits of life peculiar to those groups with highest or

TABLE VI

	Incidence %	
	Crude	Standardized w.r.t. length of Service and Age
Infantry	16·9	14·7
Armoured	10·3	9·9
Engineers	7·8	8·3
Artillery	10·6	10·6
Medical	10·6	12·6
Workshops	5·7	7·1
H.Q.s	11·9	14·8
A.S.C.	3·7	4·4
Others	5·4	6·0
All	11·6	—

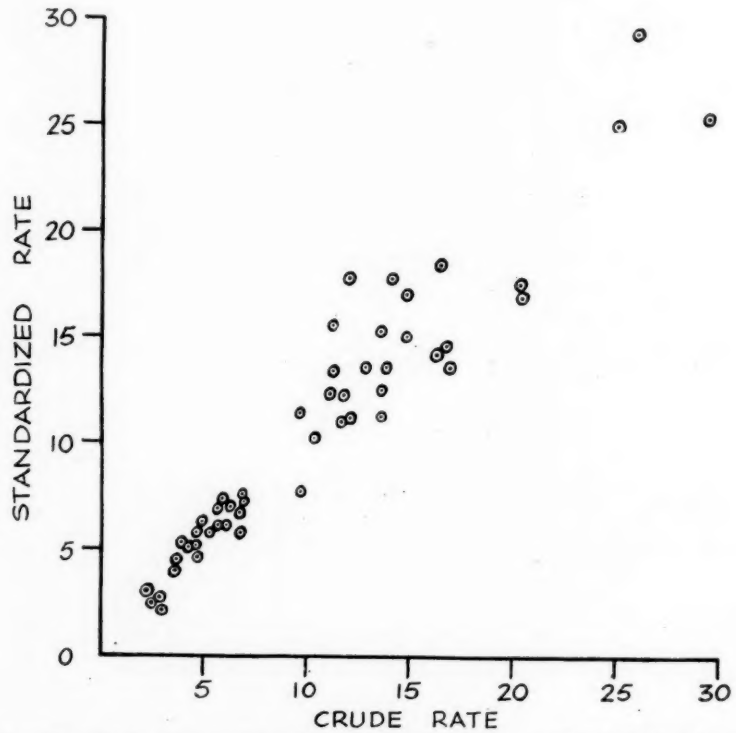

FIG. 6.—Correlation between crude and standardized rates for infective hepatitis.

lowest rates. All that we are entitled to say is that the serial order reveals no positive evidence for droplet spread as the prevalent mode of transmission.

It was also possible to make an exhaustive comparison of individual units of the division as an alternative framework of environmental differences with a view to seeking clues relevant to the aetiology of the disease. One positive result of

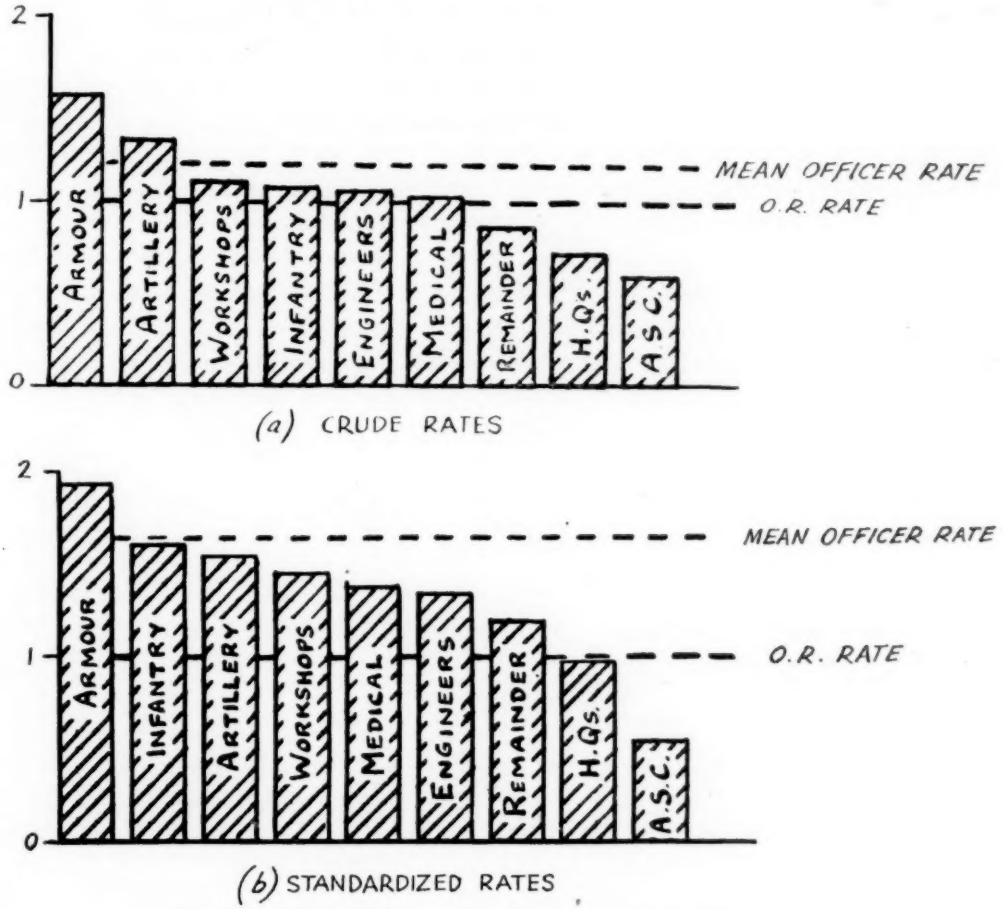

FIG. 7.—Showing the ratio of incidence rates for officers: O.R.s.

this comparison is worthy of comment. Among infantry battalions,* the only exclusively *Maori* unit had a standardized incidence of 2·4—far below the lower limit of 14·6 for others. In view of the lack of data for applying appropriate correction factors to a comparable breakdown of Canadian troops (*vide infra*) it is important to record the very close correspondence of the standardized and crude rates for individual units of the whole division. Fig. 6 shows the scatter diagram. The value of r was 0·96.

* A representative figure for the size of an infantry battalion not subject to gross variation is 800 men.

A differential statistic which attracted attention at an early stage of the war is the excessive incidence of infective hepatitis among British officers. Incidence among British officers in the Mediterranean zone has been about four times as high as among other ranks. In the New Zealand division the differential is far less striking. The crude New Zealand officer rate in the major epidemic of 1944 was only 21% higher than the rate for O.R.s, and, even when standardized with respect to age and length of service, it exceeds that of O.R.s by only 62%. Fig. 7 shows the variation of the Officer–O.R. differential according to arm of Service. On the whole, the differential is less striking in rear than in forward units.

A comparison between the differentials discussed above in respect of infective hepatitis and other major diseases of known aetiology does not disclose any correspondence sufficiently firm to justify tabulation of the results in this context. Available information also made it possible to explore the relation of severity to age, length of service in the zone, and date of onset *vis-à-vis* the course of the late 1944 epidemic. The most manageable yardstick for this purpose is duration of stay in hospital. Administrative difficulties connected with evacuation of severe cases made it inadvisable to attempt estimation of mean figures. Accordingly, the basis of comparison in Table VII is the percentage of cases remaining in hospital for more than 70 and more than 80 days. Separation of the data with regard to age and reinforcement group shows that (*a*) among new arrivals severity increases with increasing age; (*b*) among seasoned troops severity is not conspicuously dependent on age.

TABLE VII

PERCENTAGE FREQUENCY BY AGE AND REINFORCEMENT GROUP OF CASES LASTING—

(1) 70 days and over:

	Group 1–7	Group 8	Group 9+
20–	20·00	17·82	17·35
25–	14·50	23·96	18·11
30–	23·08	29·41	31·48
35–	12·90	23·08	30·56
40+	10·00	50·00	64·29
Total	16·98	21·20	20·27

(2) 80 days and over:

20–	13·33	10·89	10·34
25–	10·50	17·71	14·57
30–	14·29	20·59	17·90
35–	12·90	23·08	20·83
40+	10·00	25·00	50·00
Total	11·94	14·33	12·92

Evidence to the effect that a previous attack of infective hepatitis confers an appreciable measure of immunity to subsequent infection suggests a possible explanation of this contrast. It may well be that a previous attack which fails to confer complete immunity at least ensures that a subsequent attack will be mild.

The next table (Table VIII) indicates that for the late 1944 epidemic the severity of the disease was least at the beginning of the epidemic.

TABLE VIII

PERCENTAGE FREQUENCY OF SEVERE CASES IN EACH REINFORCEMENT GROUP AT DIFFERENT PERIODS THROUGHOUT THE EPIDEMIC

	70 Days and Over			80 Days and Over		
	June–	Sept.–	Nov.–	June–	Sept.–	Nov.–
Group 1–7 ..	13·73	20·83	12·05	7·84	15·62	8·43
Group 8 ..	16·85	22·09	23·71	11·24	15·34	15·46
Group 9+ ..	14·73	20·74	23·25	9·69	12·60	15·97
Total	14·92	20·95	21·60	9·58	13·50	14·71

INFECTIVE HEPATITIS AMONG CANADIAN TROOPS IN C.M.F.

Canadian troops selected for study were the First Corps, composed of: (*a*) an infantry division which had experienced a major epidemic during the previous season in the zone; (*b*) an armoured division which had arrived in the zone late in the previous epidemic season (winter, 1943–4) without itself experiencing a high rate of infection; (*c*) Corps troops, including units which arrived with the infantry and units which arrived with the armoured division.

Some additional data were obtained regarding base units. It was impracticable to obtain final hospital diagnoses for the sample as a whole. Hence such as follow refer to diagnoses made at field ambulance level or at casualty clearing stations. A pilot survey showed that error arising from this defect of documentation is trivial. A partial census planned to furnish basic data for standardizing crude rates had to be abandoned for operational reasons.

Fig. 8 shows the epidemiological picture for the two divisions mentioned above during the period August, 1943, to December, 1944. Two features prompt comment:

(i) The earlier arrivals (infantry division) suffered considerably less in the second (late 1944) epidemic period than in the earlier one.

(ii) The new arrivals who suffered heavily in the second epidemic season remained comparatively free from the disease during the later stages of the first epidemic, and that although sporadic cases occurred in all units of the division.

The first conclusion stated above calls for no further comment in view of its consistency with data recorded above for N.Z. troops. On its own merits, the second admits of more than one possible explanation, *inter alia*: (*a*) the virulence

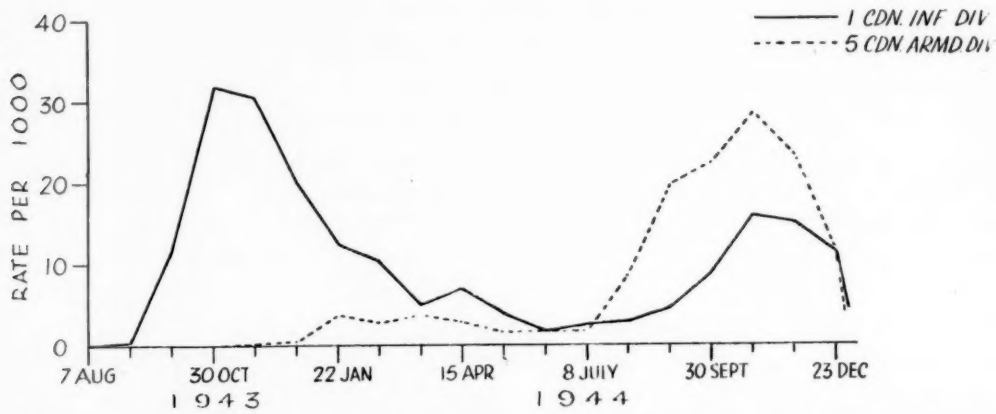

FIG. 8.—Showing incidence of infective hepatitis in 1 Cdn. Inf. Div. and 5 Cdn. Armd. Div. from time of arrival in C.M.F. until Dec. 30th, 1944 (in 4-weekly periods).

of the disease had fallen off considerably in the later stages of the epidemic; (*b*) the armoured division reached the zone at a time when conditions were not propitious to spread of the disease; (*c*) it was not engaged in active fighting like the infantry division which succumbed to the first epidemic or as were both the divisions during the second epidemic, and hence was more resistant than at a later date.

Against (*c*) we must set the fact that base troops stationed in the same area as the armoured division suffered heavily during the 1943–4 outbreak. We have no certain means of discriminating between (*a*) and (*b*) from data at our disposal.

Table IX makes possible a comparison of rates among base and forward troops during the second epidemic, when the former suffered relatively little, though situated in circumstances more favourable to droplet infection than were forward troops living largely in the open. Even within a division this difference with respect to prevalence of the disease among forward and rear troops still holds good,

TABLE IX

INCIDENCE OF INFECTIVE HEPATITIS IN VARIOUS GROUPS OF CANADIAN TROOPS IN C.M.F. DURING PERIOD JULY 1ST TO DEC. 23RD, 1944

	Population (Average Strength for Period)	Infective Hepatitis (Rate per 1,000)
5th Armoured Division	17,710	113·10
1st Infantry Division	17,260	61·06
Corps Troops	10,990	35·95
Base Troops at Avellino ..	2,005	13·9

as shown by the breakdown in Fig. 9, which exhibits monthly rates separately for Infantry, Artillery, and Services. In view of considerations advanced previously it is unlikely that the great excess of incidence among Infantry would disappear if data were available for age standardization. We might expect that units heavily affected during the first epidemic would be relatively immune to the second.

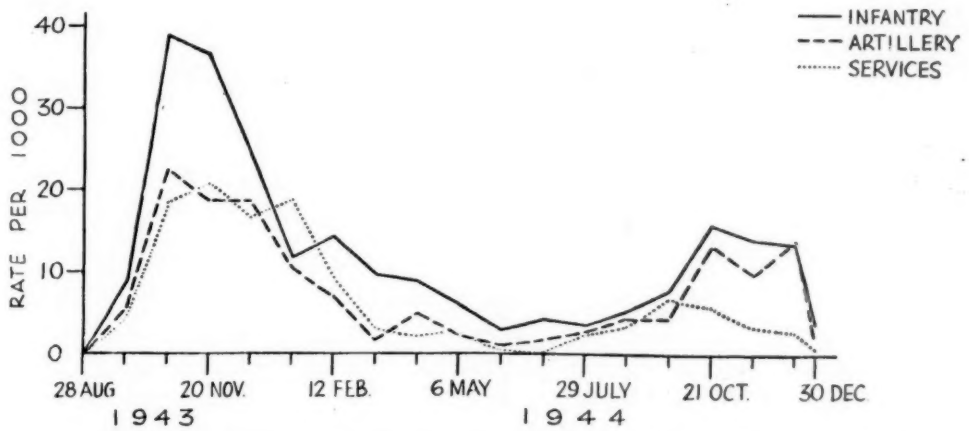

FIG. 9.—Showing the incidence of infective hepatitis in three main groups of 1 Cdn. Div. (in 4-weekly periods).

Analysis of unit rates from August, 1943, to December, 1944 failed to confirm this expectation. Comparison of such rates with rates for other diseases failed to disclose any suggestive similarities. A spurious correlation emerges in any Army statistics of this sort, on account of the fact that certain arms, more especially Infantry, have excessive incidence of all major sources of wastage.

CONCOMITANT INCIDENCE IN THE CIVIL POPULATION

Lieut.-Col. Miles, Chief of the Public Health Department, Allied Commission, Southern Region, kindly obtained for us information from medici provinciali (comparable to M.Os.H.) regarding eleven of the fifteen provinces which make up the region occupied by the autumn and winter of 1943, when Allied forces experienced an epidemic affecting all classes of troops. The medici provinciali were instructed: (*a*) to ascertain from all hospitals and doctors the number of cases of catarrhal jaundice during the period October, 1943, to February, 1944; (*b*) to make catarrhal jaundice a notifiable disease during the autumn and winter, 1944–5, and to report all cases through the normal 10-day and monthly returns of notifiable disease to the Public Health Department of Allied Commission.

Table X summarizes the outcome. During neither period was any large outbreak reported. During the 1943–4 period the largest was at Taranto, where 24 cases were reported among Italian military personnel. There is thus a striking contrast between the few cases among the civilian population and the widespread

occurrence of the disease among Allied troops of the same region in the winter, 1943–4.

TABLE X

CASES OF CATARRHAL JAUNDICE REPORTED BY 11 PROVINCES OF SOUTHERN REGION, ITALY

Province	Population (Estimate employed by Allied Commission)	No. of cases of Catarrhal Jaundice reported for period Oct. 1st, 1943–Feb. 27th, 1944	No. of cases of Catarrhal Jaundice reported for period Sept., 1944–Feb., 1945	Total	Remarks
Naples	2,175,780	—	—	—	
Bari	987,172	7	—	7	
Salerno	691,851	—	4	4	
Foggia	517,998	1	—	1	
Taranto ..	338,026	24 *	1	25	* All occurred among Italian military personnel
Lecce	514,351	—	1	1	
Cosenza ..	569,471	1	—	1	
Avellino ..	437,058	—	—	—	
Matera ..	165,950	1	—	1	
Reggio	560,371	—	17	17	
Benevento ..	339,893	3	—	3	
Total		37	23	60	

Troops of the Eighth Army entered the Northern Province of Forli in August, 1944. The force included the 1st Canadian Corps and 2nd N.Z. Division—two formations in which infective hepatitis was epidemic. These formations remained in the province until February, 1945, except for a rest period of the N.Z. troops during November, 1944. At our request Lieut.-Col. Snedeker, A.M.G., Medical Officer of Emilia Region, made catarrhal jaundice notifiable throughout the province for the period November, 1944, to January, 1945, inclusive. Once again, only trivial outbreaks were reported. Without claiming high reliability for these findings, we can safely conclude that no large-scale outbreak occurred among Italian civilians when Allied troops in the same regions experienced major epidemics. On the other hand, reports of frequent cases of infective hepatitis among Italian prisoners of war in the Western Desert are authentic (Spooner, 1943).

CONCOMITANT OCCURRENCE OF JAUNDICE AMONG SYPHILITICS

One of the outstanding problems of war medicine has been an inordinately high incidence of jaundice among syphilitics. When this inquiry began evidence was

accumulating in favour of the view that such jaundice is an infection spread by syringes employed for intravenous arsenotherapy, and it was a widespread belief that the icterogenic agent is identical with the virus of infective hepatitis. We therefore sought information concerning a relation between the two conditions. Brig. Lees, Consulting Venereologist, A.F.H.Q., kindly arranged for the circulation of a questionnaire to supply the following data for all syphilitics under arsenic treatment in V.D. clinics to the end of December, 1944:

> Personal number; rank; name; age; date of coming to Mediterranean zone (including Persia and Iraq); date of commencing arsenical treatment for syphilis; attacks of jaundice prior to treatment (with dates of occurrence); jaundice during treatment (with dates).

The results were as follows:

(*a*) The total number of patients for whom particulars were received was 872. For the vast majority of these the information was in all respects complete.

(*b*) The number of patients who developed jaundice at any time during treatment was 316—an over-all incidence of 36·24%.

(*c*) The relation of age to liability (Table XI) contrasts sharply with previous findings with respect to infective hepatitis (Table III). The contrast is entirely consonant with the conclusion of Hogben and Johnstone (op. cit.), who drew their data from the experience of troops in Britain.

TABLE XI

SHOWING AGE-DISTRIBUTION OF PATIENTS WITH AND WITHOUT POST-ARSPHENAMINE JAUNDICE AND INCIDENCE RATES IN AGE-GROUPS

Age-Group	Total Numbers in Each Group	Numbers with Jaundice	Percentage with Jaundice
18–	16	4	25·00
21–	319	116	36·36
26–	245	100	40·82
31–	164	55	33·54
36–	88	30	34·09
40+	35	10	28·57
Unrecorded ..	5	1	—
Totals	872	316	36·24

(*d*) Unlike infective hepatitis, post-arsphenamine jaundice shows no well-defined seasonal swing.

(*e*) Although the real incubation period may be shorter, we here follow the practice of previous writers who have employed the term to represent the time-interval between beginning of treatment and development of jaundice. For the

whole series (Fig. 10) the mean value, 168 days, is higher than that usually quoted. The approximate modal value is 104 days. There are, however, great individual differences, the range being from 9 days to as much as 872 days, the coefficient of variation being 62%. Of the total cases, 82% occur during the first 225 days of treatment, and 64% are concentrated in the 120 days between 76 and 195 days from commencement of treatment. The period is unaffected by differences of age and of season when treatment started. Thus the mean values for ages under 25, 26–30, and 36 and over are respectively 169, 171, and 152 days—differences which are of no statistical significance. For patients starting treatment during the four quarters of the year the means are: for January–March inclusive, 183 days; April–June, 154 days; July–September, 153 days; October–December, 172 days. None of these differs substantially from the general average irrespective of season. Although precise delimitation of the incubation period of post-arsphenamine jaundice on the basis of these data is impossible, they strongly suggest that it is significantly longer than that of infective hepatitis (21–35 days).

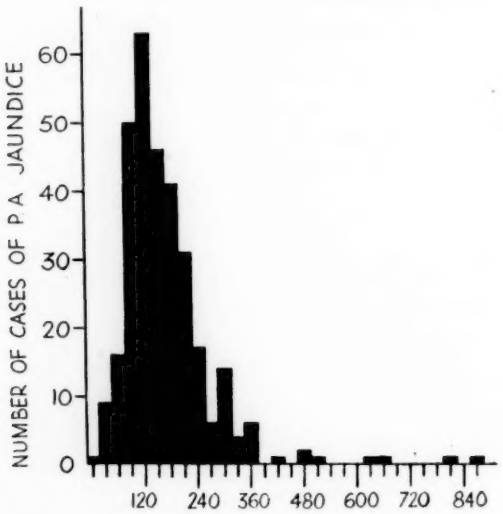

FIG. 10.—Showing the frequency distribution of the " incubation period " of post-arsphenamine jaundice.

(*f*) As regards relation of occurrence of post-arsphenamine jaundice to prior history of infective hepatitis, Table XII summarizes relevant data. Of the total, 35 (4·01%) had a history of jaundice before arsenical treatment. Of these, 12 (34·29%) developed jaundice during treatment, as compared with 304 (36·32%) of the remaining 837 with no such history. The difference is of no statistical significance. Thus a previous attack of infective hepatitis had no influence on liability to post-arsphenamine jaundice.

TABLE XII

SHOWING THE LIABILITY TO POST-ARSPHENAMINE JAUNDICE IN RELATION TO PRIOR HISTORY OF INFECTIVE HEPATITIS

	Number in Group	Number Developing Jaundice During Treatment	Percentage Incidence of Jaundice During Treatment
Patients with prior attack of infective hepatitis	35	12	34·29
Patients with *no* prior attack of infective hepatitis	837	304	36·32
Total	872	316	36·24

All the results of this part of the inquiry converge to the conclusion that the presumptive agent of jaundice accompanying syphilis treatment is not identical with the virus of infective hepatitis.

SUMMARY

1. This communication presents data bearing on epidemiological features of infective hepatitis and post-arsphenamine jaundice among Allied troops and the indigenous civil population in Italy during the late 1944 epidemic season.

2. Infective hepatitis displays striking seasonal variations, incidence being highest in autumn and winter and lowest in spring and summer.

3. Age exerts great influence on liability to infective hepatitis. Within the age limits of an Army population, liability decreases progressively with increasing age.

4. A group which has passed through a major epidemic of infective hepatitis is less susceptible than a group which has not.

5. Age-standardized incidence rates show that officers are more susceptible to infective hepatitis than other ranks.

6. Incidence differs considerably in the various arms of the Service in a division. Since forward troops are much more susceptible than base troops, droplet spread would not appear to be the most important method of transmission in major epidemics.

7. Though Italian troops suffered heavily from the disease in the Western Desert in 1942, the Italian civil population appears to have been free from any large-scale outbreak while Allied troops were experiencing major epidemics of infective hepatitis.

8. The epidemiological features of post-arsphenamine jaundice are in sharp contrast to those of infective hepatitis. Liability to post-arsphenamine jaundice is not influenced by age. It is subject to no striking seasonal variation. The

time of onset suggests a prolonged incubation period of about 100 days; and previous attacks of infective hepatitis confers no immunity. The icterogenic agent of post-arsephenamine jaundice is not the virus of infective hepatitis.

We wish to acknowledge in particular the assistance and co-operation of Brig. Kendrick, D.M.S., 2nd N.Z.E.F.; Col. King, A.D.M.S., 2nd N.Z. Division; Brig. Sinclair, D.D.M.S., 1st Canadian Corps; and Brig. Lees, Consulting Venereologist, A.F.H.Q. We also received assistance from many other medical and non-medical officers who are unfortunately too numerous for us to thank individually.

The inquiry on which this article is based was carried out under the auspices of Brig. F. A. E. Crew, Director of Biological Research, War Office.

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A STUDY OF THE HAEMATOLOGY OF 663 SUBSTANDARD RECRUITS UNDER TRAINING AT AN ARMY PHYSICAL DEVELOPMENT CENTRE

BY

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It has been the general experience of the authorities concerned, whether medical officers or not, that there is a dramatic improvement in health, physique, performance, and morale of substandard recruits who undergo a course of training at a Physical Development Centre (P.D.C.), but until recently there has been little information available about the biological criteria affected by this improvement.

During the years 1944 and 1945 an extensive piece of field research was carried out at No. 1 P.D.C., Bradbury Lines, Hereford, by the Army Department of Physical Medicine and the Army Department of Medical (Statistical) Research into the changes produced by the course of training, with a view to the correlation and evaluation of the factors involved, both physical and psychological. An immense amount of data was collected and submitted to analysis, and it is to be presumed that a comprehensive report will be published at some time, but a discussion of the general findings is outside the scope of this paper.

The haematological findings in themselves, however, provide an extremely interesting field for analysis and speculation, and this communication is confined solely to this aspect of the investigation.

It is widely recognized that group haemoglobin levels are useful criteria of general nutrition and well-being, and it appears to be tacitly assumed, even if not explicitly stated, that the higher the mean value the more satisfactory is the state of affairs. As will be shown later, this work affords some reason to doubt the validity of this assumption.

A further criterion which might prove of value in such survey work is the siderocyte level, normal values having been recently established by Case, Ladan, and Nutt (1945) for both males and females of varying age groups. The siderocyte, as an index of the number of effete erythrocytes (Case, 1943, 1945b, 1945c) should prove useful in elucidating the mechanism of any low haemoglobin values found.

Methods and Materials

In all, 663 recruits between the ages of 17 and 20 were examined on arrival at Bradbury Lines and eight weeks later when due to pass out of the station. These 663 men were the complement of three companies, of 194, 232, and 237 recruits. These figures refer to the passing-out strength, and the few who became casualties during the course, generally for traumatic reasons, are not included at all in the figures given. Of these entrants, all of whom were referred to the Centre because of " poor physique," over 80% passed out in the first grade. The term " poor physique " is almost undefinable, being a clinical opinion often compounded of several imponderables, though a careful attempt at analysing the picture was made by my colleagues when the draft arrived. The selection of the candidates was made, in two companies, by the medical officers to the units to which the recruit was drafted after conscription, and in the third company by the civilian recruitment medical board. Thus two companies were not only selected by a different process but had had approximately two more weeks' Army training and food. This may be of some significance, for, as will be shown later, two companies were drawn from exactly the same haematological " universe," whilst the third company, drafted straight from civilian life, differed very materially in haematological criteria. Nevertheless, for most of the statistical analysis, it has been considered fairer to compound all three companies into one body.

A discussion of the training at the P.D.C. is out of place in this paper, but, broadly speaking, it consisted in graded physical exercise, marches, rest periods, and adequate feeding. An analysis of the food provided in the mess (i.e., after preparation) was carried out by Dr. Robert Gaddie, of the General Hospital, Birmingham, and it was found to be very satisfactory from a calorific, vitamin, and mineral aspect. The palatability was attested by the recruits themselves, some slight monotony being almost the only criticism.

The scope of the haematological examination was as follows: (*a*) Haemoglobin estimations, before and after course; (*b*) siderocyte counts, before and after course. These were performed on all entrants. (*c*) Examination of stained films in all entrants whose initial haemoglobin fell below the arbitrary figure of 86% (100%= 14·8 grams of Hb%) before and after course. In this examination, attention was directed to anisocytosis, poikilocytosis, microcytosis, macrocytosis, and hypochromicity. (*d*) A full blood count (erythrocytes and differential leucocyte count) was performed on all recruits whose initial haemoglobin level fell below 75%. Those whose initial haemoglobin was below 86% were called " anaemics " and will be discussed later in a separate section.

The haemoglobin estimations were carried out by the alkaline haematin method of Clegg and King (1942), the alkalinized solution being evaluated on a " Spekker " photoelectric absorptiometer using an Ilford " 604 " spectral green filter and 1 cm. cells. The standard error of estimate was ±2%.

Technique of Hb Estimation

The exact technique was as follows: The middle finger of the left hand was cleaned with a cotton-wool swab moistened with ether. A tourniquet of $\frac{3}{16}$ in. rubber tubing was applied proximal to the distal phalanx, and a prick made to one side of the nail with a chisel-pointed automatic needle. (This needle was re-sharpened daily.) The tourniquet was at once released and the first small drop of blood was used to make two thin blood films on clear numbered slides. The tourniquet was again applied and a bead of blood allowed to appear. This was sucked to the mark in a 0·075-ml. pipette attached to 5 in. of $\frac{1}{8}$-in. rubber tubing fitted with a glass mouthpiece. This long length of tubing is a great convenience, as it allows the operator considerable freedom of movement. The end of the pipette was wiped on cotton-wool, the level adjusted to the mark (if necessary), and the blood blown into 7·5 ml. of N/10 NaOH solution previously placed in a boiling tube, and the alkali sucked up and down. The pipette was then removed from the tube and placed on the bench. An assistant, who was seated behind the operator and had recorded the subject's name and laboratory serial number during these proceedings, at once seized the pipette and washed it on a suction pump with water, alcohol, and ether. The whole speed of the process depends upon this assistant, and it was found possible, using only two pipettes, to alkalinize over 100 blood specimens in two 2-hour sessions on the same day.

The boiling tubes were charged with alkali before the session began, using alternately two 7·5-ml. automatic pipettes. The alkalinized blood was evaluated by the assistant, and the results read from a graph, originally calibrated with alkaline haematin made from pure haemin, checked by 40 oxygen capacity measurements made by the method of van Slyke and Neill (1924) and rechecked at Hereford against a sample of alkaline haematin supplied by Dr. E. J. King. No adjustment of the original calibration was found to be necessary.

The absorptiometer cups were filled by pipette and emptied *in situ* by a fine tube attached to the suction pump, no attempt to wash them between estimations being made, as the trace of alkalinized blood left in would cause less error than a similar amount of water, and to wash and dry between each estimation was quite impracticable.

The possibility of error arising from such factors as engorgement due to the tourniquet or cold hands was considered, and a series of control experiments showed that variations due to these causes could be ignored.

Diurnal variation was as far as possible eliminated by arranging the time-table in such a way that each section attended at the same hour on each sampling, and violent exercise before examination was avoided.

The alkaline haematin method was chosen because it is quick, reasonably accurate and free from subjective error. The Haldane-Gowers (1901) technique was ruled out because no gas supply was available, apart from any other consideration, but the results have been expressed in percentages on the B.S.I. Haldane scale (100%=14·8 grams Hb%: Macfarlane and O'Brien, 1944; King, Gilchrist and Matheson, 1944) in order to make comparison with published data easy.

It should be stressed, however, that the primary object of this investigation was to assess the effects of training upon the subjects, not to compare the results with other series, so that the fact that the method used is not that used in the Haemoglobin Survey Committee's (M.R.C., 1945) investigations is not of great moment.

It would have been impossible to make the estimations in the time available by the Haldane-Gowers technique, and, as it was, variance from technical sources was reduced to a minimum by using only two carefully calibrated pipettes, one photometer cup, and one operator evaluating the alkalinized blood.

Owing to the differences in technique employed, no statistical computations of the significance of differences of the haemoglobin values herein reported and the observations of other workers have been carried out, but such computations are justifiable in the case of the siderocyte levels, since not only was the technique the same but most of the counts were performed by the same observer.

The blood films were numbered with a diamond, dried in air, and fixed in methyl alcohol at the end of each session.

Films for siderocyte estimations were stained by the $\alpha\alpha^1$ dipyridyl-thiocyanate technique of Case (1944) and counterstained with 1% Biebrich scarlet. The slides were examined with a 2-mm. oil-immersion lens and a $\times 12$ ocular, and the siderocyte incidence estimated by counting 16 siderocytes and the distribution of non-siderocyte erythrocytes around them. The incidence is then given by the equation $f\% = \frac{m-1}{n} \times \frac{100}{1}$, where f is the frequency of the abnormal cell (siderocyte), m is the number of abnormals counted, and n is the number of normals counted during the observation. The mathematical justification for this procedure is fully discussed by Haldane (1945a, 1945b), and the method of sampling has become known as inverse binomial sampling (Tweedie, 1945; Case, 1945a). The method has the advantage of great accuracy when a small fraction of abnormals are present, and of a saving of time and labour when a large fraction exists.

The duplicate blood films from the " anaemics " were stained with Leishman's stain in the usual manner.

Results

Table I shows the means, standard deviations, and coefficients of variation of the haemoglobin values for each company before and after training, and also for the whole 663 recruits. (These parameters are calculated from the ungrouped data.)

TABLE I

Haemoglobin levels (%) in incoming and outgoing recruits

	Incoming				Outgoing		
	n	Mean	σ	V	Mean	σ	V
1st coy.	194	92·88	11·77	12·7%	99·91	7·91	7·9%
2nd coy.	237	90·73	7·68	8·5%	98·68	6·78	6·9%
3rd coy	232	99·75	9·1	9·1%	97·78	7·31	7·5%
Whole group	663	94·52	9·49	10·0%	98·72	7·31	7·4%

Table II shows the corresponding parameters for the siderocyte levels.

TABLE II

Siderocyte levels (per 1,000) in incoming and outgoing recruits

		Incoming			Outgoing		
	n	Mean	σ	V	Mean	σ	V
1st coy.	194	8·8	3·9	44·3%	4·6	2·1	45·3%
2nd coy.	237	8·4	2·9	34·9%	4·5	1·8	40·6%
3rd coy.	232	6·3	1·9	31·4%	5·0	2·0	40·4%
Whole group	663	7·8	3·0	38·1%	4·7	2·0	41·8%

Computations of the significance of the difference of the means before and after training were carried out, " Student's " (1908) " t " test being employed, and the " t " values and approximate probabilities are shown in Table III.

TABLE III

Difference and significance of difference of outgoing from incoming means of haemoglobin and siderocyte levels

	Haemoglobin			Siderocytes		
	Diff.	t	P	Diff.	t	P
1st coy.	+7·03	6·9	«0·001	−4·2	13·0	«0·001
2nd coy.	+7·95	12·2	«0·001	−3·9	17·2	«0·001
3rd coy.	−1·97	2·54	0·011	−1·3	6·87	«0·001
Whole group	+4·20	8·98	«0·001	−3·1	22·3	«0·001

Table IV analyses the difference and significance of difference of the coefficient of variation.

TABLE IV

Differences and significance of differences of V of the haemoglobin values

	Diff.	t	P
1st coy.	4·8	6·27	«0·001
2nd coy.	1·6	3·20	0·0014
3rd coy.	1·6	2·92	0·0035
Whole group	2·6	8·29	«0·001

These tables show that, with the exception of the third company, there is a highly significant rise in the mean haemoglobin value, and, in all companies, an even more highly significant fall in the mean siderocyte level. Furthermore, a significant contraction of the coefficient of variation of the haemoglobin values

TABLE V

Correlation table of haemoglobin and siderocyte levels of ingoing recruits

	Siderocytes																
Hb %	0–	2–	4–	6–	8–	10–	12–	14–	16–	18–	20–	22–	24–	26–	28–	30–	Total F_{1i}
122·5–	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
117·5–	1	0	1	2	0	0	0	0	0	0	0	0	0	0	0	0	4
112·5–	2	2	1	4	0	1	1	0	0	0	0	0	0	0	0	0	11
107·5–	1	6	6	18	5	1	1	1	1	0	0	0	0	0	0	0	39
102·5–	1	8	37	19	4	0	0	0	0	0	0	0	0	0	0	0	69
97·5–	0	4	68	32	9	4	0	0	1	0	0	0	0	0	0	0	118
92·5–	0	1	22	57	48	18	6	1	1	0	0	0	0	0	0	0	154
87·5–	1	1	5	18	46	43	11	5	1	0	0	0	0	0	0	0	131
82·5–	0	0	3	9	31	26	16	9	0	1	0	0	0	0	0	0	95
77·5–	0	1	1	6	7	2	0	4	1	1	0	0	0	0	0	0	23
72·5–	0	0	2	2	0	1	3	1	1	0	0	0	0	0	0	0	10
67·5–	0	0	0	0	0	1	1	0	0	0	1	0	0	0	0	0	3
62·5–	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
57·5–	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1
52·5–	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	2
47·5–	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42·5–	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Total F_{2i}	7	23	146	167	150	98	39	22	6	2	2	0	0	0	0	1	663

$r = 0 \cdot 82$. $b_{12} = -2 \cdot 40$ (% Hb per sid. per 1,000)

$\bar{S}b_{12} = \pm 8 \cdot 23\%$

The column and line F_{1i} and F_{2i} show the frequency distribution of Hb in 5% class intervals and siderocytes in 2 per 1,000 class intervals.

TABLE VI

Correlation table of haemoglobin and siderocyte levels of outgoing recruits

	Siderocytes								
Hb %	0–	2–	4–	6–	8–	10–	12–	14–	Total $F1_o$
122·5–	0	0	0	0	0	0	0	0	0
117·5–	2	0	0	0	1	0	0	0	3
112·5–	2	6	4	1	0	0	0	0	13
107·5–	0	36	26	5	0	0	0	0	67
102·5–	0	23	69	0	1	0	0	0	93
97·5–	1	21	175	5	2	0	0	0	204
92·5–	0	11	121	41	10	1	1	0	185
87·5–	0	0	12	21	17	6	0	1	57
82·5–	0	0	3	2	12	12	1	0	30
77·5–	0	0	1	0	2	1	3	0	7
72·5–	0	0	0	1	1	0	0	0	2
67·5–	0	0	0	0	0	1	0	0	1
62·5–	0	0	0	0	0	0	0	0	0
57·5–	0	0	0	0	0	0	0	0	0
52·5–	0	0	0	0	0	0	0	0	0
47·5–	0	0	0	0	1	0	0	0	1
42·5–	0	0	0	0	0	0	0	0	0
Total F_{2o}	5	97	411	76	47	21	5	1	663

$r = 0 \cdot 64$. $b_{12} = -1 \cdot 05$ (% Hb per sid. per 1,000).

$\bar{S}_{12} = \pm 6 \cdot 22\%$

The column and line F_{1o} and F_{2o} show the frequency distribution of Hb in 5% class intervals and siderocytes in 2 per 1,000 class intervals.

is demonstrated. The third company, however, differs materially from the other two both on incoming and on outgoing.

Tables V and VI are correlation tables of the haemoglobin levels grouped in 5% class intervals and siderocyte levels in 2 per 1,000 class intervals. From this grouped array the correlation coefficient (r) and the regression coefficient with the haemoglobin as the dependent variable (b_{12}) have been calculated in each case. There is a fairly high degree of correlation (0·82 and 0·62. n=663) in each case, but the alteration in the value suggests that other factors than an alteration of haemolytic rate, as shown by the siderocyte levels, have been at work in bringing about the altered picture. This point will be discussed later.

The haemoglobin levels in these tables have been grouped around mid-points falling on the 5 and 0 figures (e.g., 72·5—77·5 mid-point=75), but in order to facilitate a comparison with the figures of the Haemoglobin Survey (M.R.C., 1945) they have also been grouped in 5% intervals around the 2·5 and 7·5 figures. Fig. 1 shows the frequency histogram of such a grouping for the incoming and outgoing recruits and for the Haemoglobin Survey figures for single males under 20. (The tail ends of the curve have been amalgamated in larger groups.) The precise data for this comparison are shown in Table X.

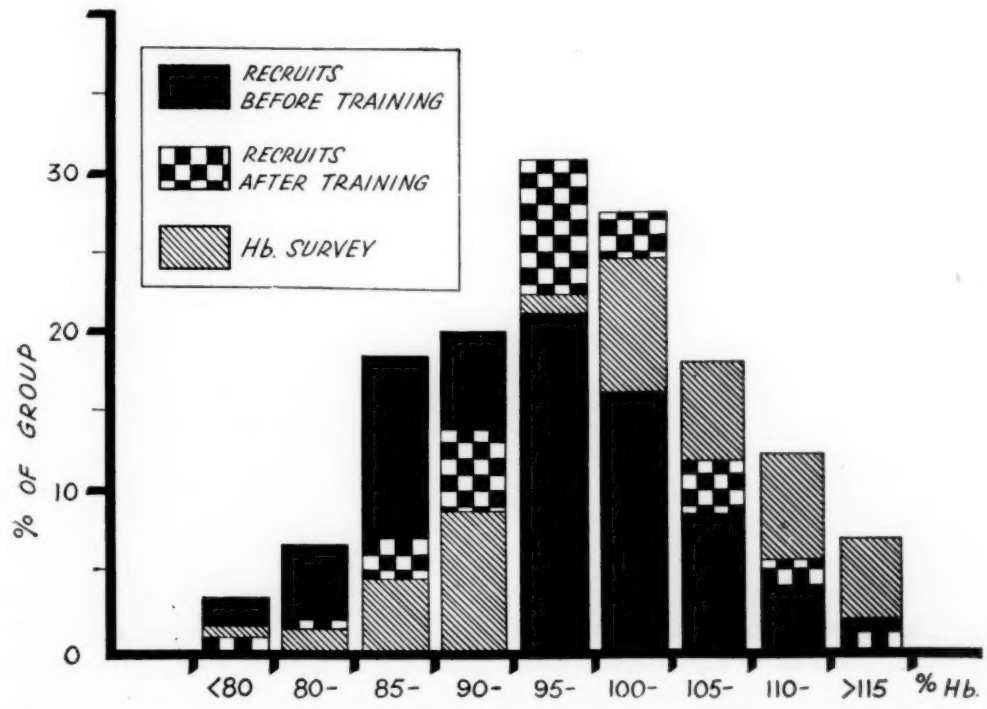

FIG. 1.—Superimposed percentage frequency distributions of haemoglobin levels, in 5% Hb class intervals, of recruits before and after training and of 489 males of the same age group. (Hb Survey data.) The actual % frequency of each group is indicated by the height of the top of the appropriate shading above the base line.

Table VII is a contingency table of the incoming and outgoing haemoglobin levels, and the extension columns show the behaviour of incoming figures in each class interval. It is shown that there is a marked tendency for incoming values above the value of the class interval of the outgoing mean to fall towards this value, whilst initially low values show a rise.

TABLE VII

Contingency table of haemoglobin levels of incoming and outgoing recruits

Hb	42·5–	47·5–	52·5–	57·5–	62·5–	67·5–	72·5–	77·5–	82·5–	87·5–	92·5–	97·5–	102·5–	107·5–	112·5–	117·5–	122·5–	Total Fl_1	Down	Stat.	Up
122·5–	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	1	0	0
117·5–	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	0	0	4	4	0	0
112·5–	0	0	0	0	0	0	0	0	1	0	0	2	6	1	1	0	0	11	10	1	0
107·5–	0	0	0	0	0	0	0	0	1	0	7	14	5	9	2	1	0	39	27	9	3
102·5–	0	0	0	0	0	1	0	0	1	0	14	28	11	11	2	1	0	69	44	11	14
97·5–	0	0	0	0	0	0	0	0	4	10	31	40	14	15	3	1	0	118	45	40	33
92·5–	0	0	0	0	0	0	0	2	5	12	46	43	28	15	3	0	0	154	17	46	89
87·5–	0	0	0	0	0	0	1	0	8	16	42	40	15	9	0	0	0	131	9	16	106
82·5–	0	0	0	0	0	0	0	1	7	14	31	24	12	5	1	0	0	95	1	7	87
77·5–	0	0	0	0	0	0	0	3	0	3	9	7	1	0	0	0	0	23	0	3	20
72·5–	0	0	0	0	0	0	0	0	2	1	3	4	0	0	0	0	0	10	0	0	10
67·5–	0	0	0	0	0	0	0	1	1	0	0	0	0	1	0	0	0	3	0	0	3
62·5–	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	1
57·5–	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1
52·5–	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	2	0	0	2
47·5–	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42·5–	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Total Fl_0	0	1	0	0	0	1	2	7	30	57	185	204	93	67	13	3	0	663	—	—	—

The column and line Fl_1 and Fl_0 show the frequency distribution of Hb in 5% class intervals. The column " Down " shows a fall from the original class interval; " Stat." remains within the original class interval; and " Up " shows a rise from the original class interval.

This point is more clearly demonstrated by Fig. 2, which shows the percentage in each incoming class interval that rise, fall, or remain within their original class interval.

Table VIII shows a comparison between the outgoing and " normal " siderocyte figures. The " normals " derived from the data of Case, Ladan, and Nutt (1945) are of 68 males aged 15-25. After training, the siderocyte levels do not differ significantly from the values for these " normals."

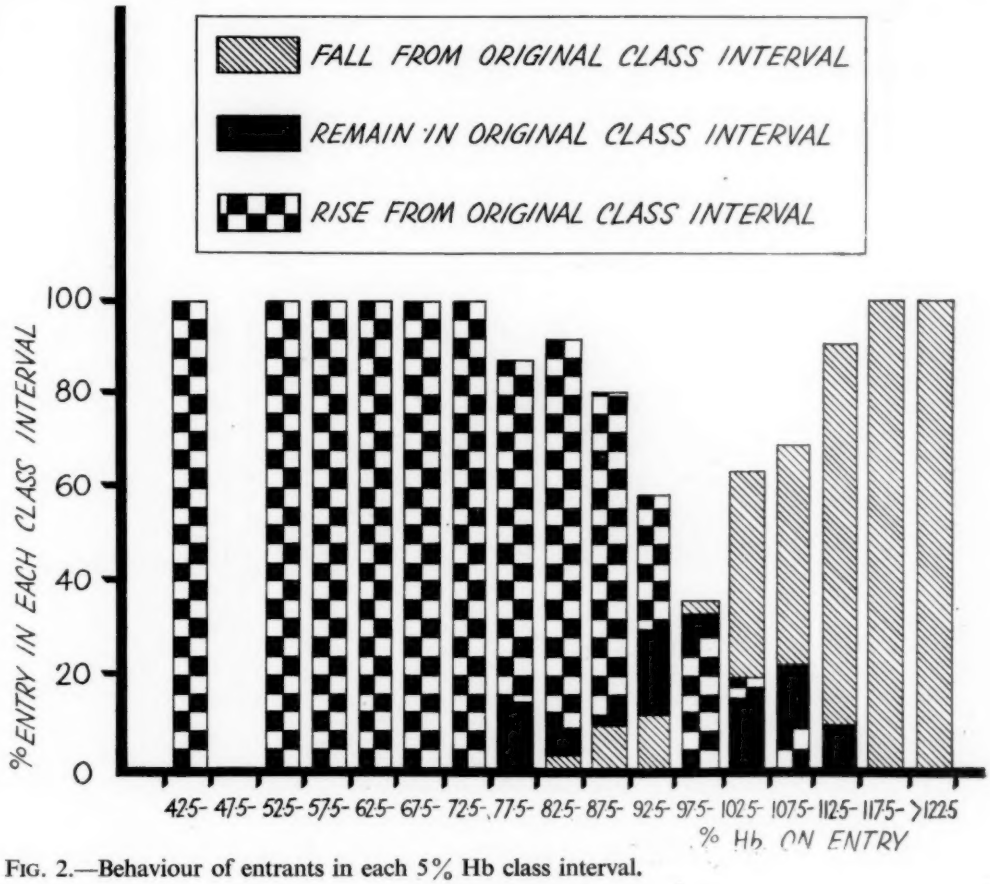
FALL FROM ORIGINAL CLASS INTERVAL
REMAIN IN ORIGINAL CLASS INTERVAL
RISE FROM ORIGINAL CLASS INTERVAL
% ENTRY IN EACH CLASS INTERVAL
100
80
60
40
20
0
425- 475- 525- 575- 625- 675- 725- 775- 825- 875- 925- 975- 1025- 1075- 1125- 1175- >1225
% Hb ON ENTRY

FIG. 2.—Behaviour of entrants in each 5% Hb class interval.

TABLE VIII

Comparison of siderocyte levels of 663 recruits, after training, with levels of 68 " normal " males age 15–25. (Data of Case, Ladan, and Nutt, 1945)

	n	mean (Sids. per 1,000)	σ	V
Recruits	663	4·7	2·0	41·8%
" Normals " ..	68	5·0	2·3	45·0%
Difference		0·3		4·2%
Significance of Difference ..		t=1·17 P=·24		t=1·05 P=·27

Fig. 3 shows the frequency histograms of the incoming, outgoing, and " normal " values in 2 per 1,000 class intervals.

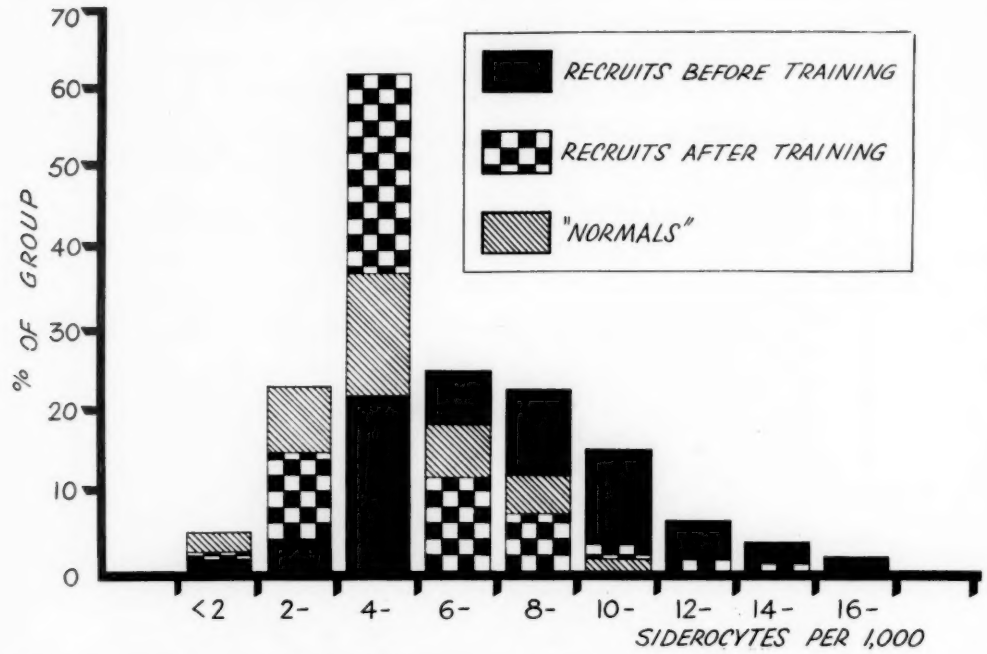

FIG. 3.—Superimposed percentage frequency distributions of siderocyte levels, in 2 per 1,000 class intervals, of recruits before and after training, and of 68 normal males of the same age group. Conventions of superposition as in Fig. 1.

Tables IX and X show the figures for the haemoglobin levels before and after training, and figures derived from the data of Davidson *et al.* (1943) and the Haemoglobin Survey (M.R.C., 1945). For sampling reasons discussed at length in the Survey, and mentioned here previously, no attempt has been made to calculate significance of differences for this data.

TABLE IX

Comparison of haemoglobin levels of 663 recruits, before and after training, with haemoglobin levels of random samples of schoolboys, students, and factory workers (male) (data of Davidson, Donaldson, Lindsay, and McSorley, 1943) and 489 single males below the age of 20 (Haemoglobin Survey Committee, M.R.C., 1945)

Group	n	Mean	σ	V
Recruits before training	663	94·5	9·49	10·0%
Recruits after training	663	98·7	7·31	7·4%
Schoolboys, 13–18	159	99·5	5·8	5·8%
Male students	100	105·5	5·1	5·8%
Male factory workers	123	100·5	6·5	6·5%
Single males below 20	489	101·7	9·2	9·0%

The parameters, apart from the means, of Davidson's data were computed from published data grouped in 10% class intervals.

TABLE X

Percentage frequency distribution in 5% intervals of recruits before and after training and single males under 20 (Haemoglobin Survey)

Group ..	<30–	35–	40–	45–	50–	55–	60–	65–	70–	75–	80–	85–	90–	95–	100–	105–	110–	115–	120–	>125% Hb
Ingoing 663 ..	0	0	0	0·15	0·15	0·3	0·15	0·3	0·6	1·8	6·6	18·5	20·0	21·5	16·1	8·6	3·8	1·1	0·5	0
Outcoming 663 ..	0	0	0	0·15	0	0	0	0	0·15	0·6	1·7	7·1	13·8	30·7	27·4	11·9	5·6	1·1	0	0
Survey 489 ..	0	0·1	0	0	0	0·1	0	0·1	0·3	0·9	1·7	4·5	8·7	22·2	24·4	18·1	12·2	4·4	1·8	0·6

TABLE XI

The effects of ferrous sulphate therapy on " anaemic " incoming recruits

		Incoming						Outgoing					
Group	n	Hb.m.	σ	V	S.m.	σ	V	Hb.m.	σ	V	S.m.	σ	V
Treated ..	51	78·4	7·2	9·2%	9·9	4·0	41%	94·6	6·3	6·7%	5·0	1·9	38%
Untreated ..	42	82·8	3·8	4·6%	11·0	4·4	40%	95·0	9·9	10·4%	4·9	2·2	45%
Difference of outgoing values								0·4		3·7%	0·1		7%
							t	0·63		2·97	0·46		1·12
							P	0·5		0·003	0·58		0·25

Discussion

For convenience it is proposed to discuss the foregoing results here, and to deal with the details of the recruits classified as " anaemics " in a separate section.

Haemoglobin Levels

The mean haemoglobin level of these recruits on entering the training centre was definitely lower than accepted standards for males of this age group (17-20). However, mean haemoglobin values seem to be associated with occupation rather than age group, and Table IX shows several groups for comparison. The recruits, on entering, were obviously drawn from a variety of occupations. During training the mean value rose considerably, and the final figure of 98·7% can probably be considered as a fairly satisfactory value. Not only does the mean value rise, however, but the scatter around the mean (coefficient of variation) is also significantly changed, becoming considerably smaller. This is brought about to a large extent by the rise of the lower values; but a second factor—the fall of initially high values—also comes into play in bringing about this contraction. This fall of the higher values is well shown by Table VII and Fig. 2, and is of interest because it gives rise to the hypothesis that under training there is a tendency to converge upon a mean value, which is perhaps physiologically more suited to the particular mode of life for which the training is a preparatory process. If further studies on similar lines should substantiate this hypothesis, then an explanation is forthcoming for the occupational fluctuation of mean values observed in the Haemoglobin Survey. It would imply that for a given mode of existence there is an optimum level of respiratory pigment, which is not necessarily the maximum observed in so-called " normal " groups.

There are several possible explanations for the mechanism whereby the reduction of the higher values is brought about, which may be summarized as follows:—

(1) Hydration balance may be a factor, the haemoglobin concentration being affected by fluid shift rather than by alteration of the total amount of circulating pigment.

(2) Faulty ventilation, due either to bad breathing habits or to variations of alveolar epithelial permeability, may have produced a compensatory rise, which is corrected by improved oxygenation after training.

(3) A true dynamic haematological imbalance may have existed, which is corrected by a haemolytic process overtaking the haemopoietic process until an optimum level is reached. This process could be brought about by retardation of haematopoiesis with no change in haemolytic rate, by acceleration of destruction of erythrocytes with no increase of haematopoiesis, or by both mechanisms at work simultaneously.

(4) More than one of these processes may be at work at the same time, since the explanations are not necessarily mutually exclusive.

A comparison of the observed values for the recruits before and after training with data on large groups of males collected by other workers show that under training, the haemoglobin values approximate fairly closely to those of males of the same age group, with the reservations inherent in the occupational fluctuation, and also reveals that before training a disproportionately large percentage of the recruits had low haemoglobin values (Tables IX, X, and XII), but that after training this figure is much the same as in the males under 20 examined in the Haemoglobin Survey.

Siderocytes

The siderocyte is an ageing erythrocyte, and appears to be a good index of the percentage of erythrocytes being removed from the circulation at any given time (Case, 1943, 1945b). A study of these cells should therefore provide some information about the dynamics of the erythron in such groups of subjects as we are now dealing with. Normal levels have been established (Case *et al.*, 1945) and the raw data are available for comparison purposes.

In the incoming recruits, the siderocyte mean is shown to be raised, but after training the picture is not significantly different from that presented by the normals previously studied. The mean and coefficient of variation approximate very closely, and the distribution graphs are very similar.

The correlation coefficients of the siderocytes and haemoglobin levels are of interest. On incoming, the coefficient is high, suggesting that much of the variance of Hb levels is explained by haemolytic processes, but after training, when the siderocyte picture is normal, the correlation has dropped, which suggests that other mechanisms are at work—a possibility adumbrated above.

The coefficients of regression calculated from the grouped data are of value, since, with their corrected standard errors of estimate ($\overline{S}b_{12}$), they allow of a forecast

of the amount of change of Hb level expected per unit siderocyte change if the factors involved remain constant. A study of the observed changes and calculated changes will help in elucidating the number of mechanisms at work. This technique will be used in the section dealing with the " anaemics."

The significance attached to the difference of the various parameters of the siderocyte figures for the incoming and outgoing recruits is greater than that attached to the difference of the haemoglobin parameters, and this suggests that the siderocyte might be an even more sensitive indicator of the effects of training than the haemoglobin levels themselves, though obviously it is still better to use both indices.

Homogeneity of Material

The entrants were divided into three sections. As has been previously mentioned, the first two sections were selected by the same methods, and had had about 14 days' previous training before entering the P.D.C. The third section was selected by a different type of selection board, and arrived without any preliminary training whatsoever.

The haemoglobin and siderocyte figures for the third section differ very materially from those of the other two sections, which, statistically, may be regarded as being drawn from the same haematological universe. The third company came in with a much higher haemoglobin mean, which actually fell under training, but with a lower siderocyte mean, which fell under training to the same value as the other sections. Furthermore, some members of the third company actually became " anaemic " during the training period (see below).

There was no reason to suppose that the third company differed from the remaining companies in social and occupational background, so it would seem probable that the differences found must be attributable to differences in the mechanism of selection or to the alteration in time relationship of the training period to the observations (or to both these factors).

There is, of course, no evidence in these data concerning the first of these alternatives, but there are indications that the second concept may play a quite considerable part in the observed phenomena. The third company, with a lower haemolytic tendency as shown by the siderocyte levels, came in with a higher haemoglobin mean, including a fairly large number of high values which decreased, and a number who actually became " anaemic " during training. If the hypothesis of the convergence upon an optimum mean related to the environmental conditions is sound, it may well be that such mechanisms as are brought into play do not at once establish the desired equilibrium state, but tend to overact at first, causing an oscillation around the optimum, possibly of progressively decreasing magnitude. This hypothetical optimum does not interfere with the concept of diurnal variation, being itself subject to such change. It is possible that the extra 14 days' training (25% of the total time) was a sufficient length of time to allow the adjusting forces to come into play and produce the discrepancies in the incoming observations,

and that the magnitude of the oscillation had decreased sufficiently in the final 14 days to allow the observed difference to occur.

Studies on " Anaemics "

As previously stated, for the purpose of this research, all recruits who on entry returned a haemoglobin value of less than 86% were arbitrarily classified as " anaemics," and were made the subject of more extensive studies. These studies are, in fact, a detailed investigation of the low-value tail of the distribution curve of the haemoglobin levels.

In addition to the investigations discussed under " Methods," these " anaemics" were divided into two approximately equal groups, and 9 grains of ferrous sulphate administered daily for a period of 30 to 50 days to one group. The division into groups was intended to be random, but there is some reason to believe that there was a slight bias in favour of treating the worst anaemics (i.e., those with the lowest levels) with iron, this bias being connected with " ethical " considerations.

Results.—Table XI shows the effect of iron therapy upon the anaemic group receiving ferrous sulphate contrasted with the behaviour of the control group of anaemics who were not so treated. Apart from a smaller coefficient of variation in the outgoing levels of the iron-treated recruits, there is no evidence that the exhibition of iron influenced the behaviour of the haemoglobin values, and, since both groups improved markedly under training, this means that there is here no evidence of an iron-deficiency anaemia requiring iron supplementary to the amount provided in the diet. The figures do not, of course, show that iron deficiency played no part in the aetiology of the anaemia, since the diet contained reasonable amounts of iron, but, since the improvement took place so quickly without supplementing the diet, any such deficiency must have been of a minor degree.

TABLE XII

Incidence of anaemia in recruits before and after training, and in males under 20 in Haemoglobin Survey

	Before Training	After Training	Hb Survey
<86% Hb	93 (14·0%)	25 (3·8%) (8 residual)	3·8%
<76% Hb	11 (1·7%)	2 (0·3%) (1 residual)	0·6%

Table XII shows the incidence of " anaemia " in the recruits before and after training compared with the incidence of " anaemia " in the Haemoglobin Survey's series. Before training there was a marked preponderance of low levels, but after training the incidence was much the same as in the Survey's group.

Of the 93 anaemics of the incoming group, only 8 were " anaemic " at the end of the training period, and of the remaining 570 recruits who were not " anaemic " on entry, 17 became anaemic during the course; 14 of these 17 were from the third section.

Table XIII shows the details of the 17 entrants who became " anaemic " and also shows the behaviour of the haemoglobin levels calculated from the regression coefficients of the whole group, and the residual deviations (z^1) from the expected behaviour. This analysis shows that 4 out of 17 cases lie outside one standard deviation of the residuals and 1 outside two standard deviations on the calculations based on the incoming data. This is much what would be expected if the association of siderocytes and haemoglobin contributed the same amount to the erythron dynamics in each case. From the second calculation, based on the outgoing data, the observed differences of haemoglobin exceed the calculated differences by more than one standard deviation in 10 out of 17 cases, by more than two standard deviations in 5 cases, and three standard deviations in 1 case. This is much more than is expected if the interplay of causes is similar in the " anaemics " and the recruits after training.

It therefore appears that these entrants who became " anaemic " during training show a similar haemoglobin–siderocyte pattern to the whole body of recruits

TABLE XIII

Details of 17 recruits who became " anaemic " during training

Coy.	Hb_i %	Hb_o %	S_i per 1,000	S_o per 1,000	Hb_o-Hb_i %	S_o-S_i per 1,000	Hb diff. calculated A ±8·23	Hb diff. calculated B ±6·22	Residuals " z^1 " z^1A	Residuals " z^1 " z^1B	Remarks z^1A	Remarks z^1B
1	95	85	6	11	−10	+5	−10·8	−5·25	+ 0·8	− 4·75	<σzA	<σzB
2	88	85	7	8	− 3	+1	− 2·4	−1·05	− 0·6	+ 1·95	<σzA	<σzB
2	86	85	9	9	− 1	+0	0	0	− 1	− 1	<σzA	<σzB
2	89	82	9	11	− 7	+2	− 4·8	−2·1	− 2·2	− 4·9	<σzA	<σzB
3	93	81	9	5	−12	−4	+ 9·6	+4·2	+31·6	+16·4	>3σzA	>2σzB
3	87	80	9	9	− 7	+0	0	0	− 7	− 7	<σzA	>σzB
3	103	83	5	11	−20	+6	−14·4	−6·3	− 5·6	−13·7	<σzA	>2σzB
3	103	72	5	11	−29	+6	−14·4	−6·3	−14·6	−22·7	>σzA	>3σzB
3	87	76	9	9	−11	+0	0	0	−11	−11	>σzA	<σzB
3	89	83	9	9	− 6	+0	0	0	− 6	− 6	<σzA	<σzB
3	91	83	7	12	− 8	+5	−10·8	−5·25	+ 2·8	− 2·75	<σzA	<σzB
3	97	81	4	13	−14	+9	−21·6	−9·45	+ 7·6	− 4·5	<σzA	<σzB
3	99	85	5	10	−14	+5	−10·8	−5·25	− 3·2	− 8·75	<σzA	>σzB
3	105	85	4	10	−20	+6	−14·4	−6·3	− 5·6	−13·7	<σzA	>2σzB
3	99	83	4	5	−16	+1	− 2·4	−1·05	−13·6	−14·95	>σzA	>2σzB
3	95	85	7	10	−10	+3	− 7·2	−3·15	− 2·8	− 6·85	<σzA	>σzB
3	99	85	5	11	−14	+6	−14·4	−6·3	+ 0·4	− 7·7	<σzA	>σzB
3	95	85	6	11	−14	+5	−10·8	−5·25	− 3·2	− 8·75	<σzA	>σzB
M	94·4	82·3	6·65	9·65							<σzA 13 >σzA 4 >2σzA 1 >3σAz 1	<σzB 7 >σzB 10 >2σzB 5 >3σzB 1
					Diff. of −12·1	Means +3	− 7·2	−3·15	− 4·9	− 8·95	17	17

Calculated Hb differences A and B are computed from the regression coefficients $b_{12}=2·40$. $\bar{S}b_{12}=\pm 8·23\%$ and $b_{12}=-1·05$. $\bar{S}b_{12}=\pm 6·22\%$. $\sigma z=\bar{S}b_{12}$.

before training, but little similarity to the after-training picture. Since the great majority of these groups are drawn from the third section, this finding lends some support to the time–relation theory already outlined.

Table XIV shows the details and a similar analysis of the 8 recruits who remained "anaemic" throughout the course. Here the observed differences agree equally well with differences computed from each regression coefficient, in each case 2 out of 8 lying outside one standard deviation and 1 outside two standard deviations. In fact, the observed differences tend to lie between the two sets of calculated differences, suggesting that the training has brought about only a part of the change observed in the bulk of the entrants.

TABLE XIV

Details of 8 recruits, initially "anaemic," who remained so

	Hb$_i$ %	Hb$_o$ %	S_i per 1,000	S_o per 1,000	Hb$_o$-Hb$_i$ %	S_o-S_i per 1,000	Hb diff. calculated A ±8·23	Hb diff. calculated B ±6·22	Residuals "z^1" z^1A	Residuals "z^1" z^1B	Remarks z^1A	Remarks z^1B
	79	79	6	8	0	+ 2	− 4·8	− 2·1	+ 4·8	+ 2·1	<σzA	<σzB
	58	76	10	6	+18	− 4	+ 9·6	+ 4·2	− 8·4	−13·8	>σzA	>2σzB
	69	78	13	8	+ 9	− 5	+12·0	+ 5·25	+ 3	− 3·75	<σzA	<σzB
	82	81	10	10	− 1	0	0	0	− 1	− 1	<σzA	<σzB
	81	82	14	12	+ 1	− 2	− 4·8	− 2·1	+ 3·8	+ 1·1	<σzA	<σzB
	77	83	13	8	+ 6	− 5	+12·0	+ 5·25	+ 6·0	− 0·75	<σzA	<σzB
	46	48	30	8	+ 2	−22	+28·8	+12·6	+26·8	+10·6	>3σzA	>σzB
	85	85	11	11	0	0	0	0	0	0	=	=
M	72·1	76·5	13·4	8·9	Diff. of Means +4·4	−4·5	+10·8	+4·7	+6·4	+0·3	<σzA^6 >σzA^2 >2σzA^1 >3σzA^1	<σzB^6 >σzB^2 >2σzB^1 >3σzB^0
											8	8

Table XV shows the cytological analysis of the 93 "anaemics," subdivided into those receiving iron therapy and those not receiving it.

Both on entry and outgoing, the "anaemics" fell quite naturally into three classifications—normochromic normocytic anaemias, hypochromic normocytic anaemias, and hypochromic microcytic anaemias. These diagnoses were made on microscopical criteria, it not being practicable to make haematocrit or cell diameter studies. The table shows the cytological improvement resulting from training, and again reveals that iron therapy does not appear to have influenced the end result.

TABLE XV

Cytological analysis of 93 " Anaemics "

Incoming									Outgoing								
+$FeSO_4$ Therapy					−$FeSO_4$ Therapy				+$FeSO_4$ Therapy					−$FeSO_4$ Therapy			
	n	A	P	A+P	n	A	P	A+P		n	A	P	A+P	n	A	P	A+P
N.N.	24	0	0	0	21	1	0	0	N.N.	24	0	0	0	21	0	0	0
									H.N.	0	0	0	0	0	0	0	0
									H.M.	0	0	0	0	0	0	0	0
H.N.	20	3	2	1	7	1	1	1	N.N.	14	0	0	0	4	0	0	0
									H.N.	6	0	0	0	3	1	1	1
									H.M.	0	0	0	0	0	0	0	0
H.M.	7	5	2	2	14	5	1	1	N.N.	4	0	0	0	12	0	0	0
									H.N.	0	0	0	0	0	0	0	0
									H.M.	3	2	1	1	2	1	1	1
Total ..	51	8	4	3	42	7	2	2		51	2	1	1	42	2	2	2

		In	Out		In	Out
Total: both groups	N.N. ..	45	79	A ..	15	4
	H.N. ..	27	9	P ..	5	3
	H.M. ..	21	5	A+P ..	4	3
	n ..	93	93			

N.N.=Normochromic normocytic. H.N.=Hypochromic normocytic. H.M.=Hypochromic microcytic.
A=Anisocytosis. P=Poikilocytosis. A+P=Both present. (A subject showing A+P would be entered under A,P and A+P.)
All the outgoing subjects showing A,P or A+P were residual from their original group.

Table XVI shows the detailed cytological analysis of the 11 " anaemics " who entered with a haemoglobin below 76%. Of these, one was probably a case of " splenic anaemia " and one gave a history of recent exposure to lead hazard. In one, the white cell picture was abnormal, and this was the only abnormality in differential counts noticed in the whole anaemia investigation.

Discussion of the " Anaemic " Recruits

A rather unexpectedly high proportion of the recruits were found to have haemoglobin levels below 86% on admission (93 out of 663=14%), and a much smaller fraction (11 out of 663=1·7%) fell below 76%. After the course, the

TABLE XVI

Cytological analysis of 11 " anaemics " below 76% Hb

Hb_i %	Hb_o %	S_i per 1,000	S_o	E_i	E_o	M.C.H.$_i$	M.C.H.$_o$	W.B.C.$_i$	W.B.C.$_o$	P_i	L_i	O_i	P_o	L_o	O_o	$FeSO_4$	
55	101	20	4	3·8	4·7	21·6	31·5	10·0	9·5	65	34	1	58	39	3	+	
74	93	4	4	3·9	4·5	27·9	30·0	7·4	10·2	70	28	2	65	34	1	+	
68	110	19	4	4·4	4·9	22·5	30·0	8·3	7·4	60	38	2	62	38	0	+	a
70	87	10	8	3·7	5·1	28·0	25·5	14·8	14·2	90	8	2	85	12	3	+	b
53	90	14	4	3·5	5·0	22·1	26·8	9·3	9·4	55	45	0	60	38	2	+	
73	102	6	3	3·8	4·7	26·0	33·0	7·3	10·0	72	18	0	65	34	1	+	
58	76	10	6	3·0	5·3	28·5	22·0	7·3	7·4	58	40	2	65	33	2	+	c
73	97	6	5	3·8	4·0	28·0	35·5	10·3	6·0	60	38	2	70	28	2	+	
69	78	13	8	4·0	3·2	25·5	35·0	11·2	10·9	65	34	1	70	27	3	+	
64	95	17	5	3·8	5·0	25·0	29·0	10·5	11·7	70	27	3	62	38	0	−	
46	48	30	8	2·7	2·7	25·0	26·0	5·3	4·8	50	48	2	55	45	0	−	d

E=Erythrocytes in 10^6 per c.mm. W.B.C. in 10^3 per c.mm. M.C.H. in $\mu\mu$g.
P=Polymorphs %. L=Lymphocytes %. O=Others %.
a=Recent history of lead hazard.
b=Absolute and relative polymorphonuclear leucocytosis.
c=Became very hypochromic histologically.
d=Suspected of " splenic anaemia."

incidence was 25 (=3·8%) and 2 (=0·3%). Of these, 8 and 1 respectively were residua from the original " anaemics," the others having fallen below the critical value during the course.

The " anaemias " were of " simple " type, about half being originally normochromic normocytic, over one-third being hypochromic normocytic, and the remainder hypochromic microcytic. After training, the blood picture was normochromic and normocytic in 79 out of the 93 cases, and hypochromic microcytic in only 3 instances. Anisocytosis and poikilocytosis were rather rare findings.

The white cell picture was remarkably normal in these " anaemics," only one abnormal picture—a relative and absolute neutrophil polymorphonuclear leucocytosis—being found. One case had a rather low total white count. This was the most severe and resistant anaemia of the whole group, and was thought to be a " splenic anaemia." One anaemia was thought to be possibly associated with lead hazard.

Iron deficiency of any marked degree was excluded as an aetiological factor in the production of the " anaemias " by giving adequate therapeutic doses of iron (ferrous sulphate, 9 grains daily for 30 to 50 days) to about one-half of the " anaemics." Apart from a lower coefficient of variation in the treated group, there was no difference in the end-result in the two groups.

Another unexpected finding was that 17 cases who came in with haemoglobin values over 85%, of whom 7 were over 95% and 3 over 100%, went out with haemoglobin values of less than 86%. It is of considerable interest that 13 of these 17 cases came from the third company, whose differences from the remaining two

companies have been discussed. A comparison of the observed fall in haemoglobin values and that calculated from the haemoglobin–siderocyte regression coefficients suggests that the factors working on the haematological equilibrium are similar in their quantitative results to those obtaining in the " non-anaemics " before training, rather than to those after training. It seems possible that this technique of residual estimation from a haemoglobin–siderocyte regression holds possibilities in haematological investigations.

A similar analysis of the " hard core " of anaemics suggests that the dynamics of their haematological equilibrium lie between that of the incoming recruits and that of the outgoing ones.

Summary

A study of the haematological picture of 663 substandard recruits under training has been made, using haemoglobin estimations, siderocyte counts, stained films, and in some cases full blood counts. Many further data, such as social background and family history, were collected during the investigation, but it is outside the scope of this communication to attempt to correlate these, and this discussion is purely haematological in its treatment.

On starting the course the recruits had a rather low (94·5%) haemoglobin level, with a high proportion (14%) of values below 86%. After training the mean had risen to 98·7%, and the incidence of low values had fallen to 3·8%. These latter figures are very similar to the figures obtained by the Haemoglobin Survey (M.R.C., 1945) for a random sample of males of the same age.

Not only did the haemoglobin mean rise during training, but the scatter around the mean, expressed as the coefficient of variation, also diminished significantly. At the same time there was a marked tendency for values to converge upon a modal point at the level 97·5%-102·5%. This converging tendency gives rise to a hypothesis that there may be an optimum haemoglobin level associated with the occupational environment.

The siderocyte levels on entrance were raised (7·8 per 1,000), but fell to " normal " values (4·7 per 1,000) after training. There was a high degree of correlation between the siderocyte levels and the haemoglobin levels, and regression coefficients were calculated before and after training. These coefficients were used to calculate the expected behaviour of the haemoglobin values of some groups of recruits, and a possible method of analysing some of the factors affecting haematological equilibrium was developed.

The " anaemias " were investigated and found to be " simple " normochromic normocytic, hypochromic normocytic, or hypochromic microcytic in type. Most of them improved markedly under training, but the administration of ferrous sulphate to about half of them had no effect. However, the diet was not deficient in iron.

Conclusions

1. The haemoglobin levels of substandard recruits sent to a Physical Development Centre were found to be low on arrival (94·5% "Haldane") with a rather large coefficient of variation (10%).

2. An unexpectedly large number of the recruits (14%) showed values of less than 86%, being anaemias of "simple type," mainly normochromic normocytic, with some hypochromic normocytic and hypochromic microcytic types.

3. The siderocyte levels of the recruits on arrival were raised (7·8 per 1,000).

4. After training, the haemoglobin mean had risen to 98·7% and the coefficient of variation contracted to 7·3%. These figures approximate very closely to the Haemoglobin Survey's figures for males of the same age group.

5. After training, the incidence of figures below 86% had fallen to 3·8%, which is the same as that reported in the Haemoglobin Survey. Some cases (17), mainly from one company, which differed in several respects from the other two, fell from higher levels to below 86%.

6. There was a marked tendency for initially high values to converge upon a mean, suggesting an optimum value for these recruits fitting them for the conditions imposed by the training.

7. The administration of iron as ferrous sulphate was without effect on the "anaemics," a control group improving to exactly the same extent.

8. After training, the siderocyte level had fallen to 4·7 per 1,000, which is not significantly different from that of males of the same age group.

9. Both before and after training, haemoglobin and siderocyte levels show a high degree of correlation.

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